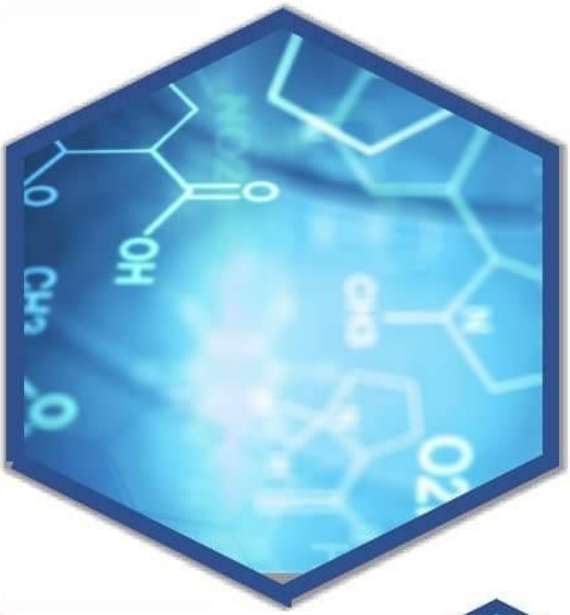
PHARMA ORGANIC



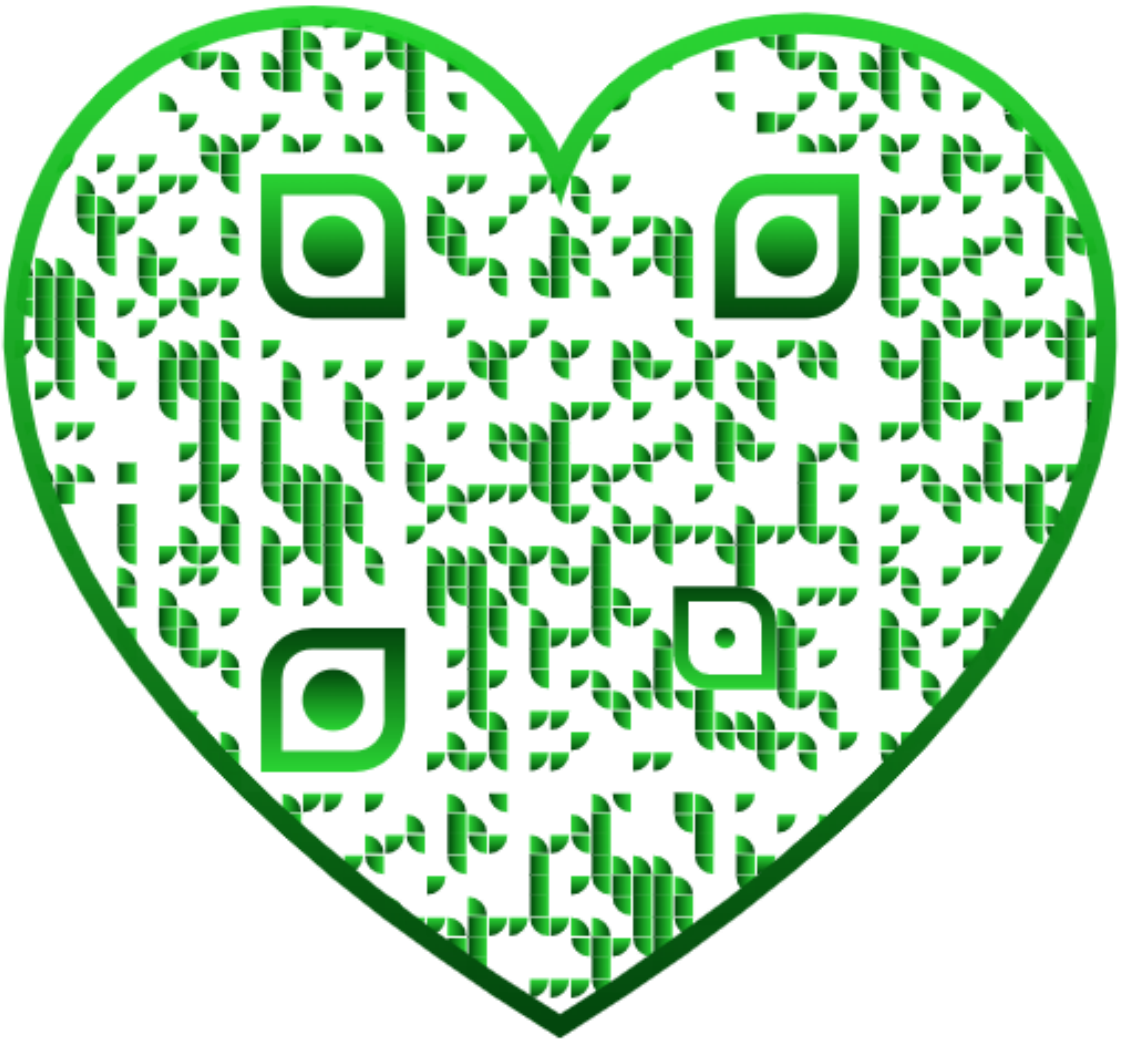
Metabolism
part 2

pharmacgy
فارمسجي

Done By:

Mohammad Hamzeh

Aya Fuad & Lujain Thalji



Metabolism-part 2

We have already discussed a large part of the subject, and we talked lastly about the C-heteroatom systems, specifically the C-N system, and we discussed every functional group that contain the C-N bond (aliphatic and cyclic and even the aromatic)

And in a general we said that this system has 2 main reactions:
1- Reaction at the alpha carbon to the heteroatom 2- reaction at the heteroatom itself (only N&S).

Also remember, in each oxidation reaction there has to be an H at the site where the reaction would occur >> what actually happen is the O is inserted between the C and H bond (C-H) to become (C-OH)

- **حكينا عن ال c-heteroatom system وحكينا انها عبارة عن c متصلة مع N,O,S وشرحنا أطول واصعب اشي اللي هو النيتروجين وهسا رح نكمل مع O وS**

The C-O system

The C-O system reactions are only on the alpha carbon; (we cannot oxidize the O)

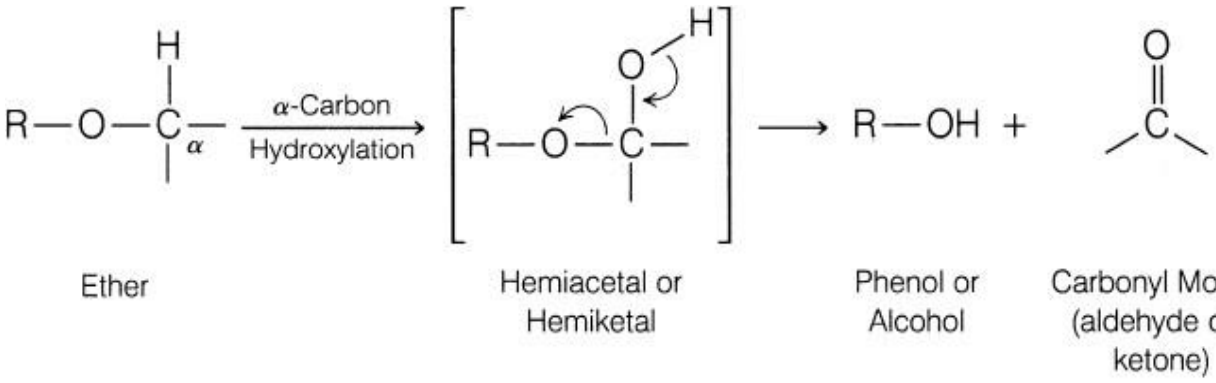
- **حكينا قبل انه عملية oxidization بنعملها ع (C,N,S) فقط ما بصير نعملها ع الاكسجين**

- **Search in the drug for any (C-O) bond, with the condition that the alpha carbon has hydrogens.**

The only is reaction (oxidative O-dealkyation)

Let's see what happens.

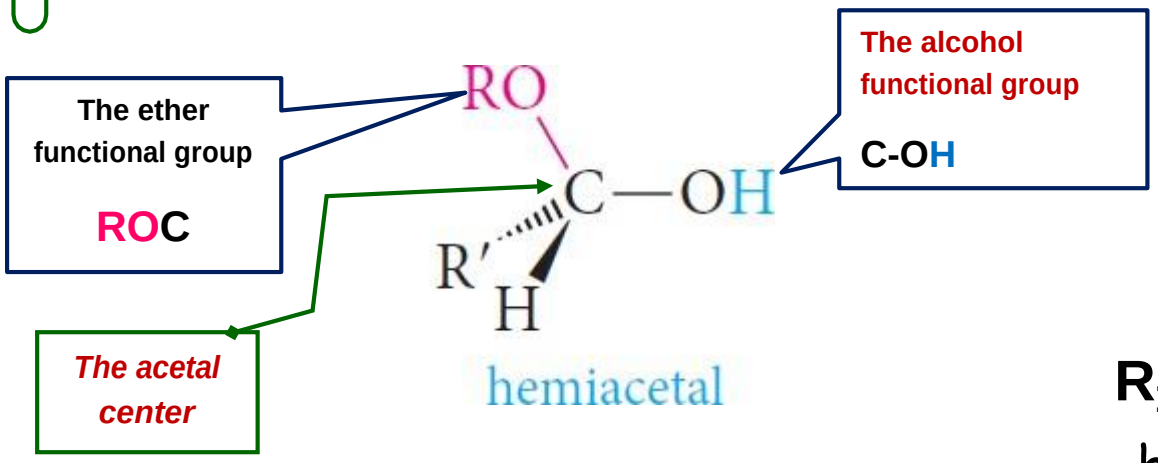
الاكسجين الها تفاعل واحد فقط و بشبه التفاعل اللي بحدث لل N

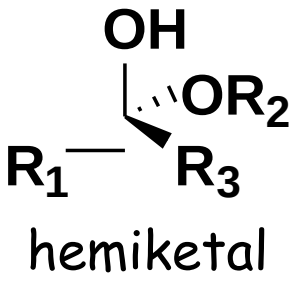


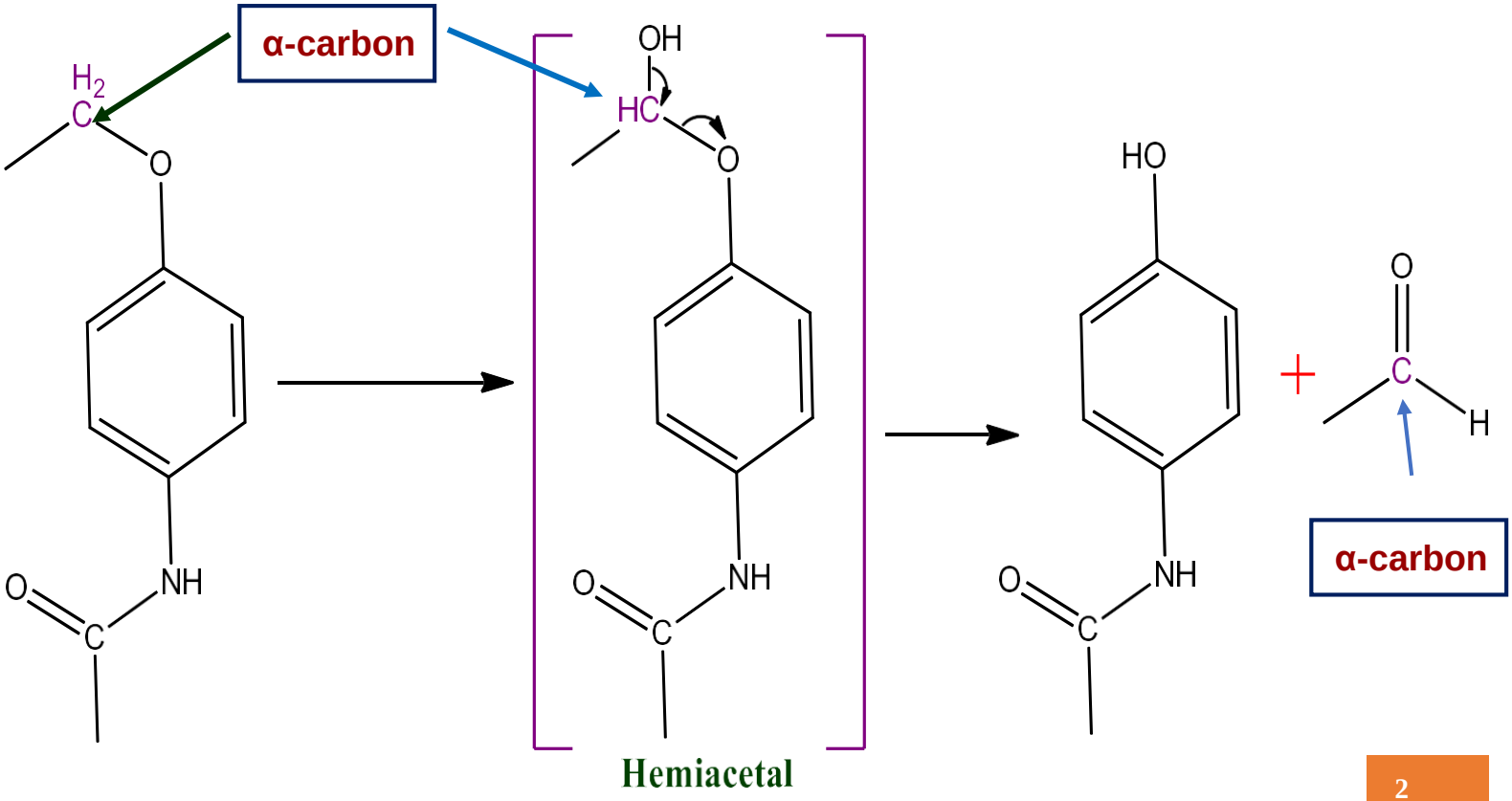
The O is inserted between the alpha carbon and H, and an intermediate is formed. The intermediate can be a "Hemiactal" or "Hemiketal"

A hemiacetal or hemiketal, contain both alcohol and ether functional groups on the same carbon atom
The carbon connected to the two functional groups is called the "*acetal center*"
>>the carbon attached to 2 Oxygens is called the acetal center.
Now if the acetal center is attached to 2 R groups it is called hemiketal (from ketone)
If the acetal center is attached to an R group and Hydrogen, then it is called hemiacetal

ال Hemi ketal او Hemi acetal بتكونوا من كحول وايثر , الفرق بينهم الكربونة اللي بتتصل بذرتين O بتكون acetal
center , بحال كانت acetal center متصلة ب R و H بتكون Hemi acetal
اما اذا كانت متصلة ب 2R بتكون Hemi ketal





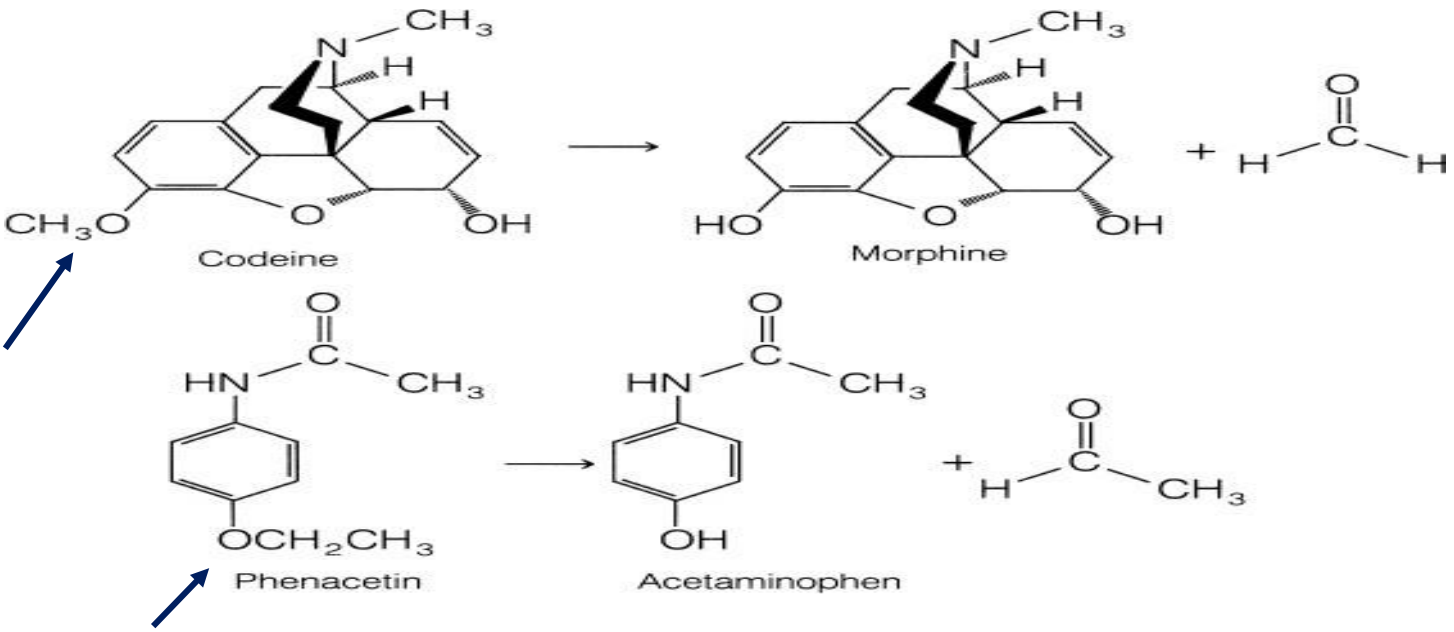


نفس طريقة تفاعل النيتروجين لكن هون اخذنا الالفا كاربون اللي برا الحلقة مش تاعت الحلقة ليش ؟؟
بنرجع وبنحكي لانه ما معها H عندها اربع روابط بالتالي ما بتقدر تعمل التفاعل

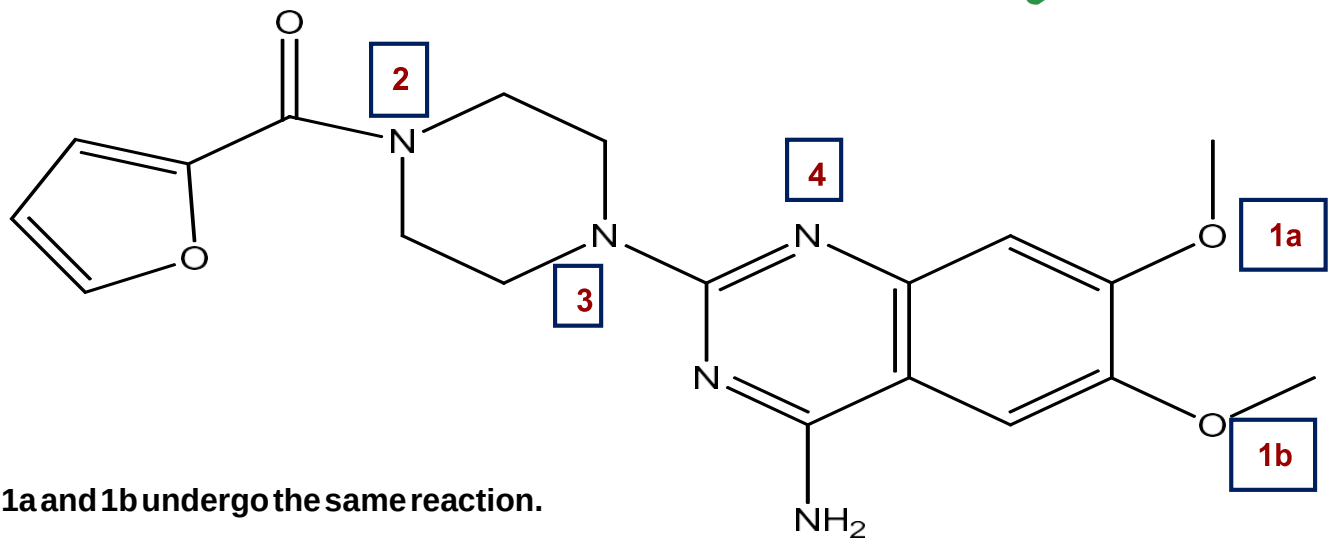
Notice the secondary amine, can it undergo oxidative N-dealkylation??
If your answer was yes, then you are mistaken, no alpha hydrogens.

- بهاد السؤال قصده عن مجموعة الأمين الموجودة بالمركب السابق فهي لا تستطيع ان تقوم بتفاعل **oxidative N-Dealkylation** ليش ؟؟

لانه **2 alpha carbons** اللي عليها ما عليهم الفا هيدروجين واحنا حكينا انه هاد التفاعل ما بتم الا بوجود الالفا هيدروجين.



المركبات مش للحفظ بس عشان نتدرب ع طريقة الحل



1a and 1b undergo the same reaction.

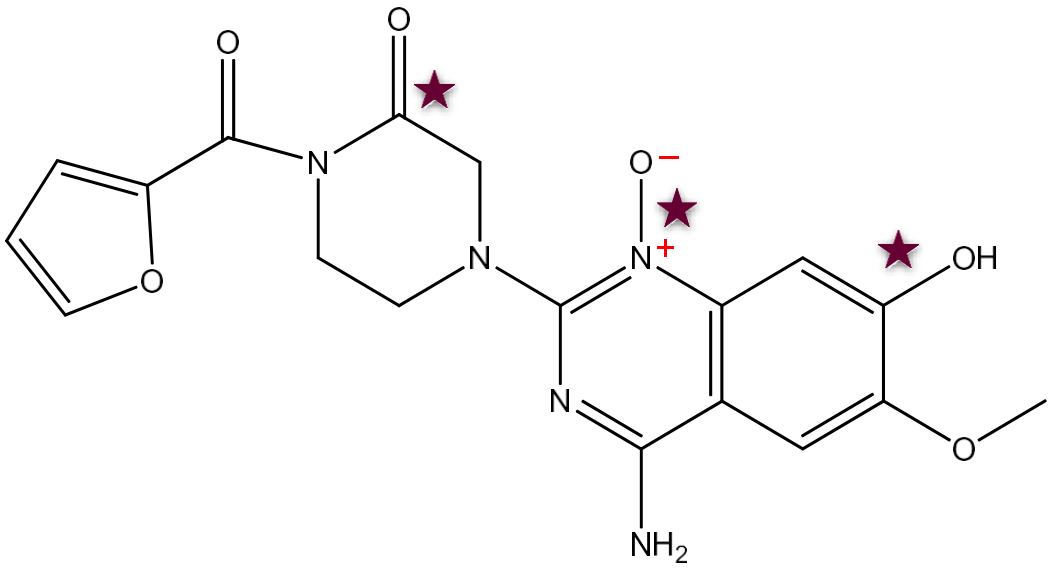
Choose any of them (1b can be the 1st step and 1a can be the 2nd step) we said before there can be more than 1 metabolic reaction but each one occur one step at time >> oxidative O-dealkyation.

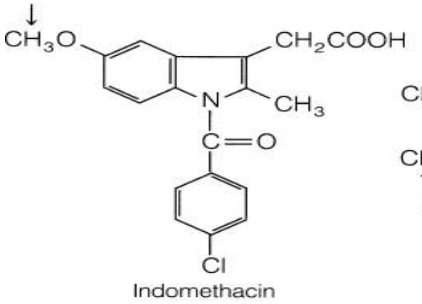
#2 is the same as #3>> both have alpha carbons with alpha H's >> the alpha carbon is oxidized to a (C=O)

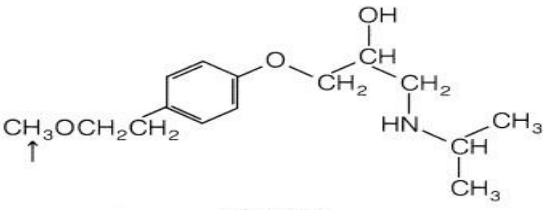
#4>> it would be oxidized to an O-oxide

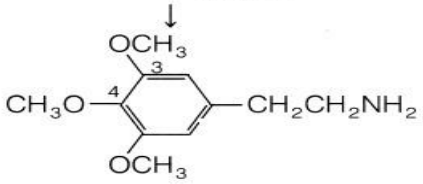
This would be the product after 3 steps

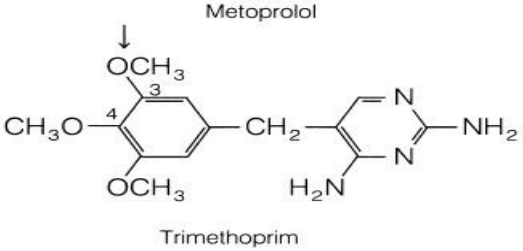
(each reaction was in a step of its own) not together











only oxidative O-dealkylation

The C-S system

there are 3 reactions to this system:

1- Oxidative S-dealkylation

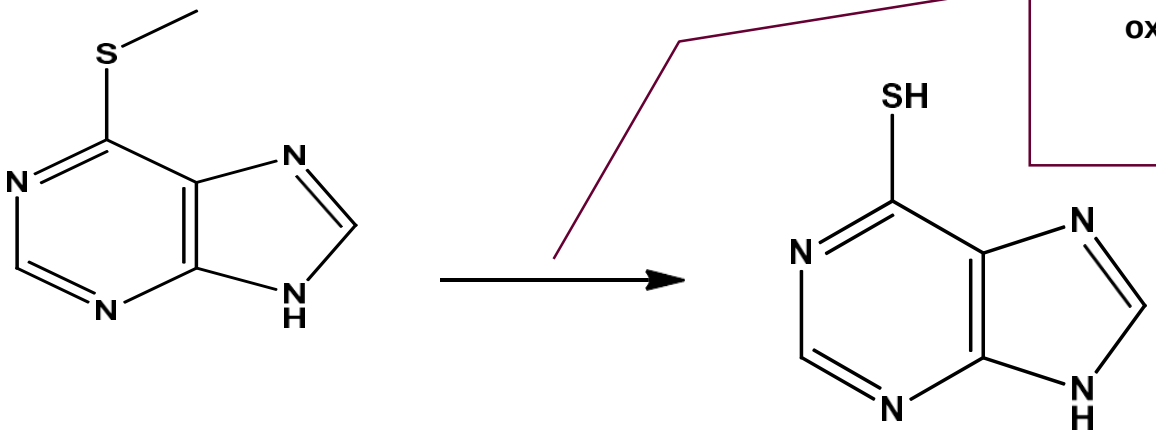
This reaction occurs on the α-Carbon and it lead for an R group to leave the Drug > by the cleavage of the C-S bond.

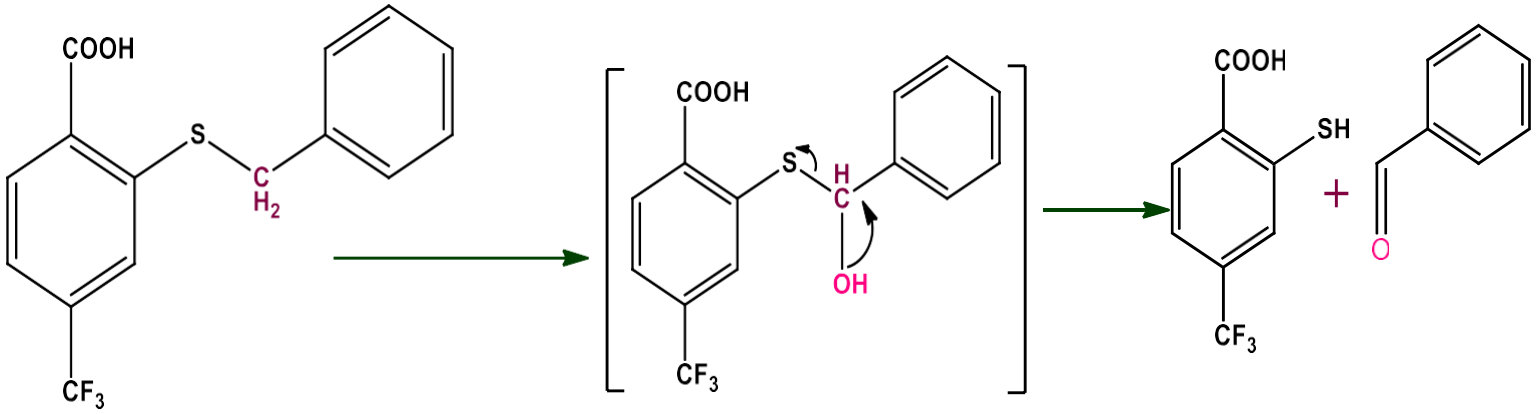
بنشيل مجموعة الالكيل وبنحط مكانها هيدروجين.

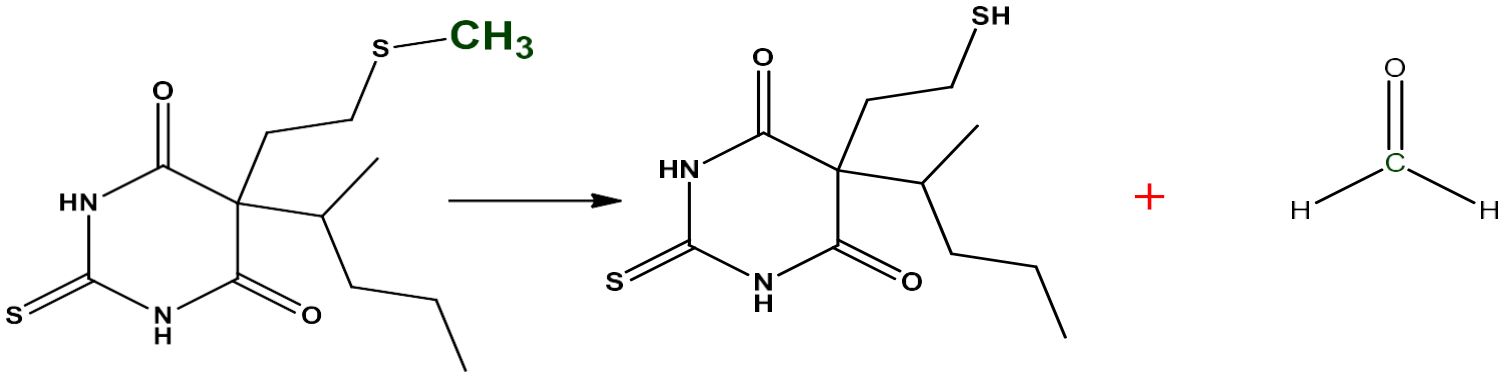
The same mechanism as the oxidative N-dealkyation

(no intermediate)

كلهم نفس طريقة التفاعل



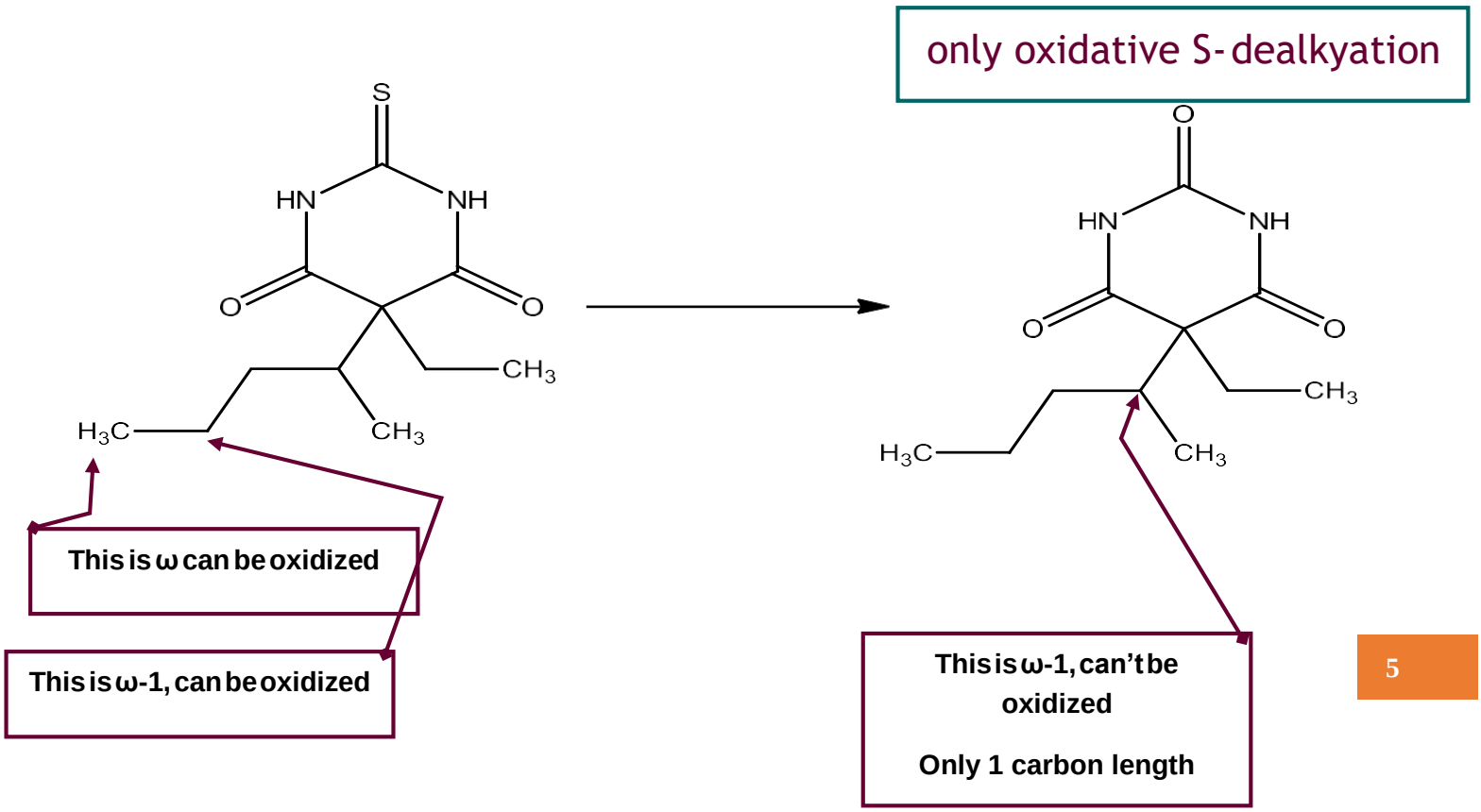




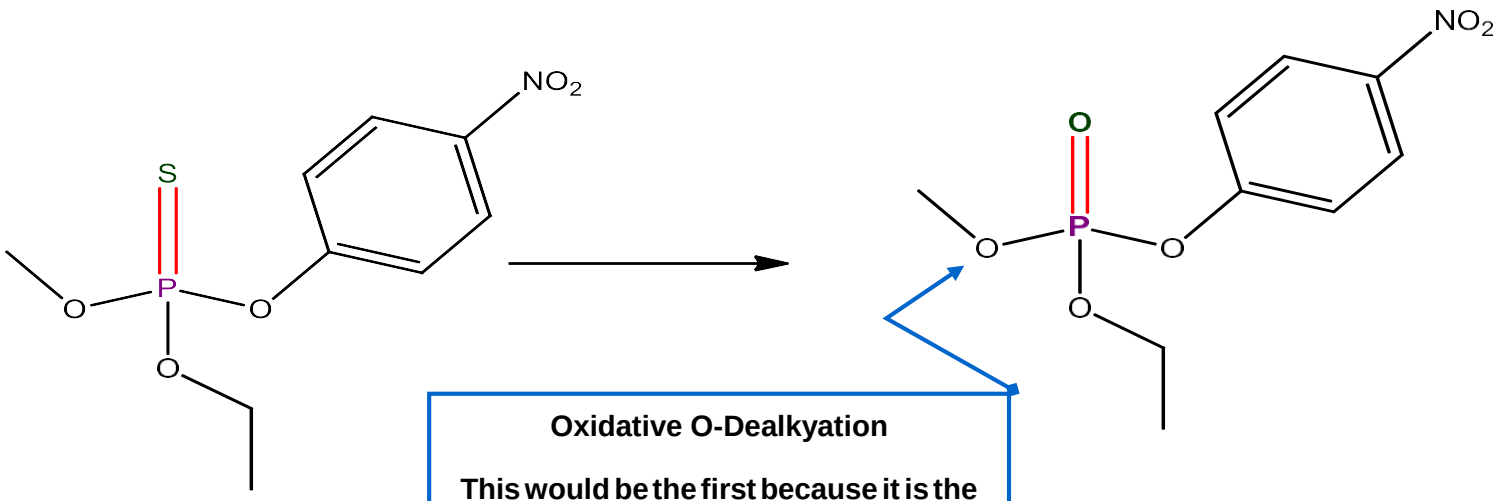
2- Desulfuration

Which is a reaction, to convert the sulfur-carbon double bond or (C=S) to carbon-oxygen double bond (C=O).
The (S=P) bond can converted in the same way to (P=O).

يعني بس بنشيل S وبنحط مكانها O.



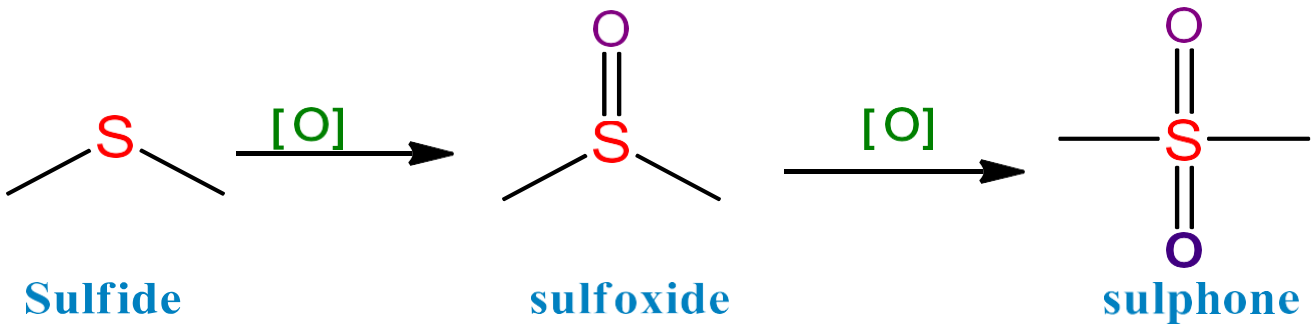
يفضل ترجعوا للريكورد دقيقة 20 بريكوردات محمد حمزة بارت 2 الريكورد الأول



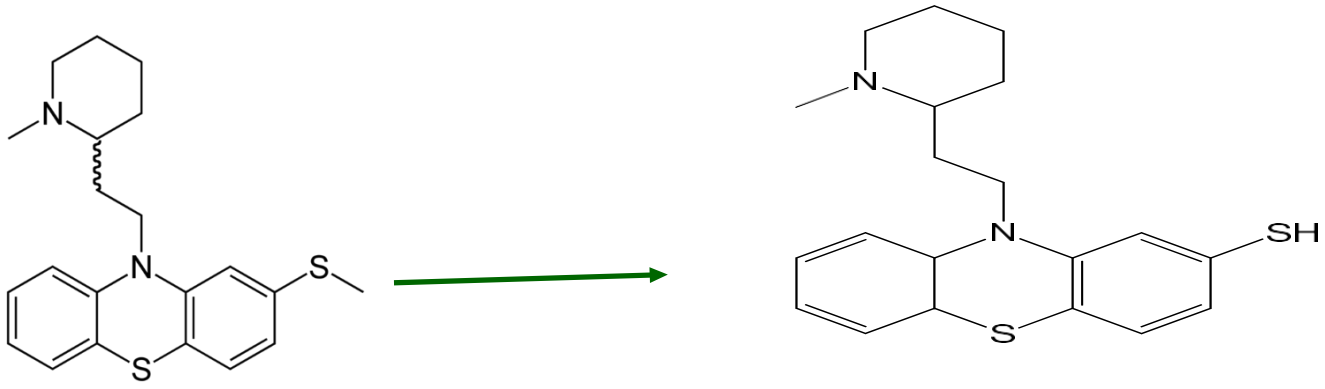
بكل بساطة C=S بتتحول ل C=O و P=S ل P=O

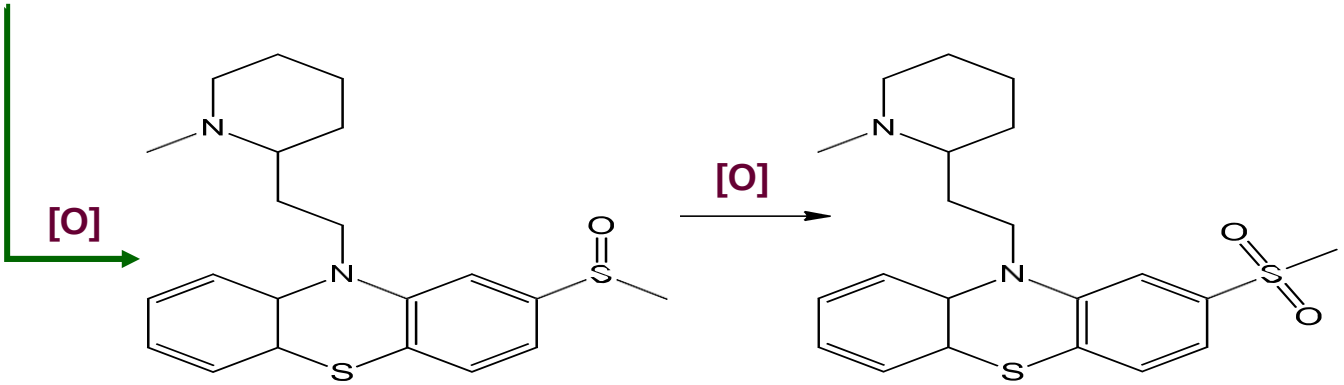
3- S -Oxidation reactions

If a sulfur is between 2 R groups (-S-) then it can be oxidized as the following:ا



Sulfide اذا كانت مرتبطة بمجموعتين ممكن يصيرلها oxidation وبتكونلنا 2 products الأول sulfoxide والثاني sulphone

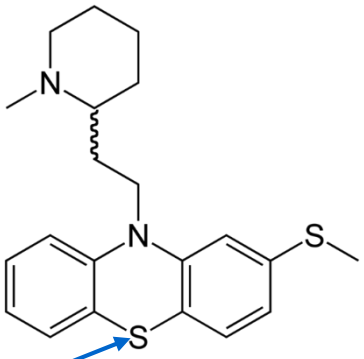




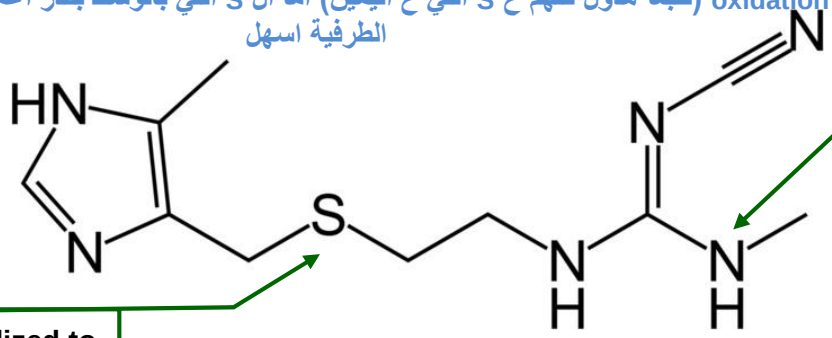
In the compound above there are 3 products in total

The one from the oxidative S-dealkyation and the 2 from the S oxidation

Now, this can be oxidized but only after the terminal S because it is less bulky



هاد المثال بصير عنا 3products الأول بنتج من dealkylation والثاني من oxidation 1 والثالث من oxidation 2 (طبعا هدول كلهم ع S اللي ع اليمين) اما ال S اللي بالوسط بقدر اعملها oxidation لكن الطرفية اسهل



Can be oxidized to Sulfoxid and sulphone

Cannot undergo deamination reaction

Because the α-C before it has no α-H's

Oxidation of Alcohols and Aldehydes:

Alcohol is produced from different metabolic pathways such as oxidation of benzylic, allylic, alicyclic or aliphatic oxidation.

If the OH is not conjugated (has a double bond adjacent to it(OH-C=R), it will further oxidized.
Primary alcohol and aldehydes give facile oxidation to carboxylic acid.

Less important, secondary alcohol to ketone, not that important as it may be reduced again to alcohol as it is easier to be conjugated

The enzyme called alcohol dehydrogenase (when here the word dehydrogenase, it is an enzyme that catalyze redox reactions) perform reversible reaction that converts alcohol to aldehyde and ketone, using NAD^+ as a coenzyme

❖ هاد الانزيم بكون موجود بتفاعلات تحويل الكحول ل الديهايد او كيتون

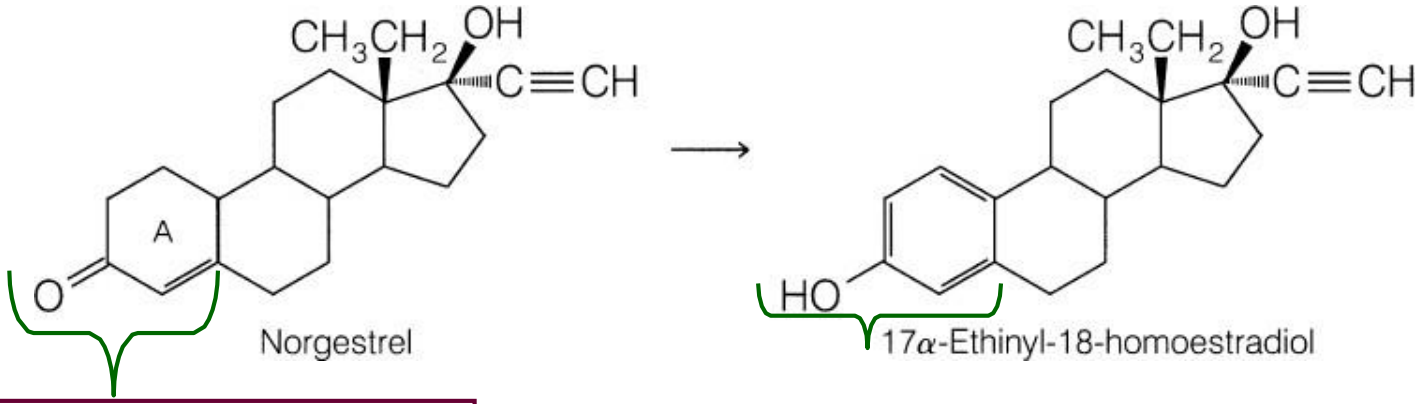
Further oxidation of aldehyde to COOH, is done by aldehyde oxidaze and xanthine oxidize
Enzyme are not be memorized.

Other Oxidation Reactions

We have finished the oxidative reactions, and now we are going to take some examples that are not under any of the other reaction (you should know them well)

التفاعلات اللي رح نحكيها هسا مش مطلوب نعرف الميكانيزم بس لازم نعرف اسم كل تفاعل والمتفاعلات والنواتج

The reaction we are going to discuss are observed in the body and we should know the general scheme of them.



Memorize this structure

an allylic carbonyl carbon or (α,β unsaturated ketone) within a six member ring

دبل وبعدها برابطة مجموعة كربونيل

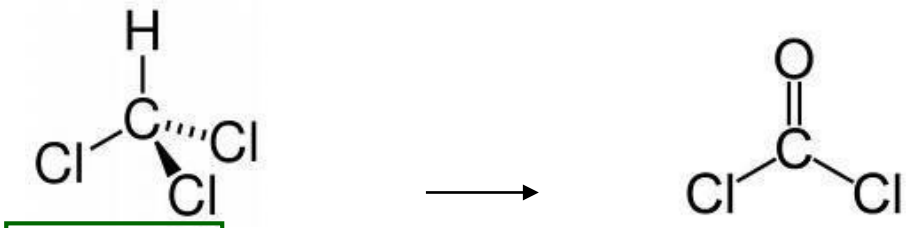
It becomes a phenol

اول كربونة متصلة بالكربونيل تسمى الفا ثم الكربونة التي تليها بيتا وبكون بينهم (=) فهم unsaturated وبكونوا ضمن حلقة سداسية

This type of reaction is called, oxidative aromatization

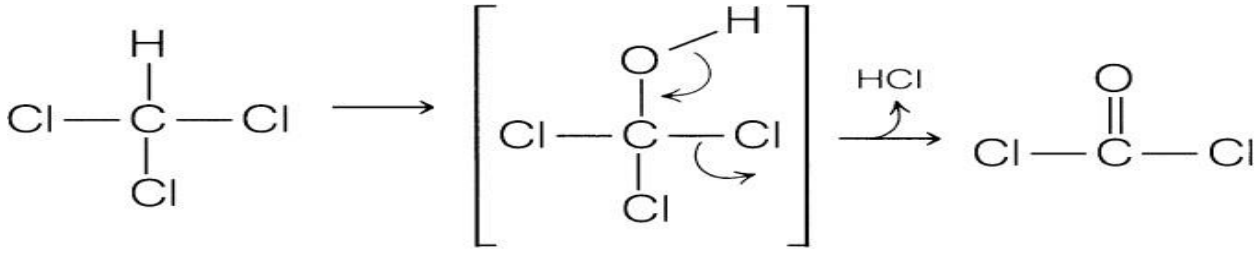
Another type is called, oxidative dehalogenation.

As the name indicates, this is a reaction that removes a halogen from the drug via oxidation.



Chloroform **phosgene**

Chloroform produce phosgene (an acyl halide>>very reactive, which causes hepatotoxicity and nephrotoxicity).



First the O get inserted and form the intermediate; it can do so because it has a hydrogen
Second step, is for the Cl to leave group; as it is a good leaving group (GLG), has a large size (stable) and weak base.

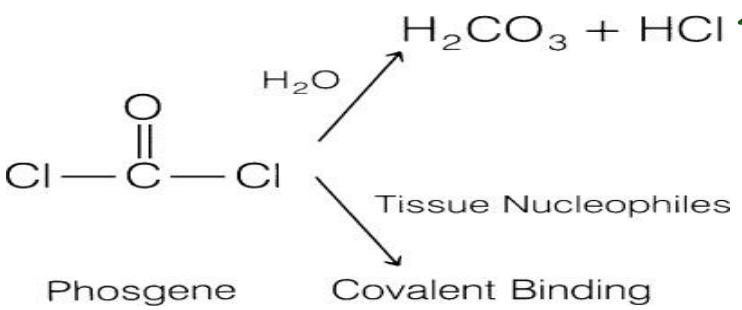
The product formed is called "phosgene" (important, memorize)
This product is very reactive and can be toxic, look at the carbonyl carbon >it has 2 Cl (EWGs) and thus the carbonyl carbon is very electrophilic and that's why this compound is very reactive.

- هاد المركب نشاطه كثير عالي ليش؟؟ لانه مرتبط بمجموعتين EWGs شو يعني ؟؟ يعني انه هاي المجموعات بتسحب الالكترونات من الكربون فبتخلي عندها نقص كبير بالالكترونات بالتالي بتقلل من استقرارها فنشاطها بزيد

طيب احنا شو بدها بهالحكي كله هسا ؟!! اللي بدنا نعرفه انه بما انه المركب كثيير نشط فما رح يستنى الانزيم حتى يكمل التفاعل رح يروح يتفاعل مع macromolecules (DNA,RNA,protins) الموجودة بالجسم ويتسبب بحدوث كانسر☹☹

****

The phosgene (فوس جيين) has to routes to continue, of both it reacts with a Nu.



The 1st route is to react with H2O and form carbonic acid (H2CO3) and this is considered good route

The 2nd route (if H2O is not there) is to react with one of the macromolecules and may lead to cancer and this is a bad route

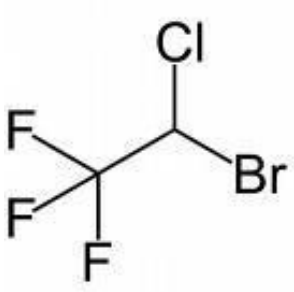
اسمعوا الريكورد الأول من دقيقة 30 رح يساعدكم تفهموا هاد التفاعل كثيير منيح والتفاعل مهم جدااا

Normally dehalogenation reactions produce toxic acylhalides

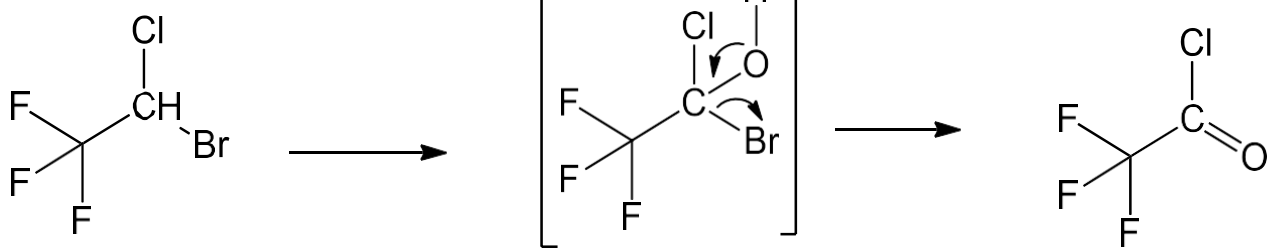
What are your ideas on this compound?

Can it under go oxidative dehalogenation??

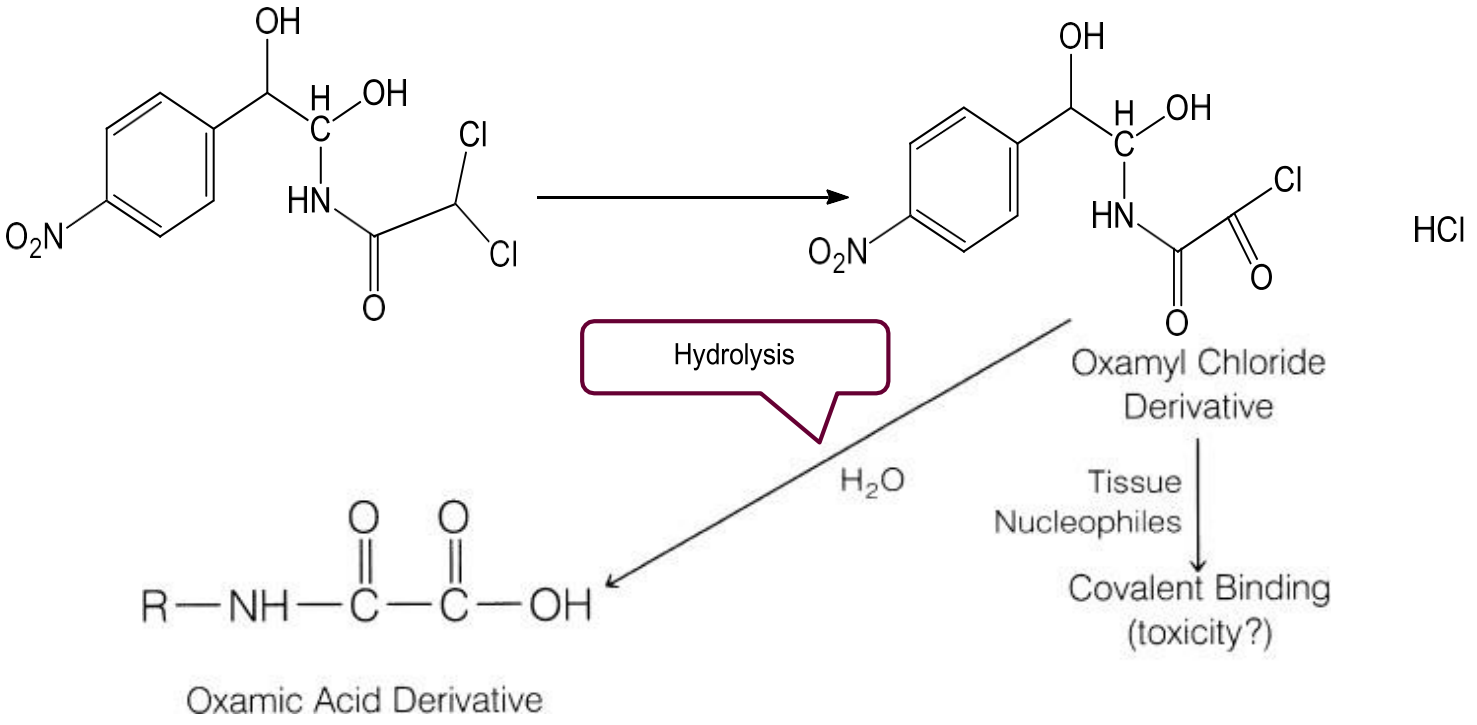
For that to happen it need to have carbon with an (H) on it and a halogen (or any GLG at least)



this compound does have the conditions for oxidative dehalogenation, so let's its reaction.

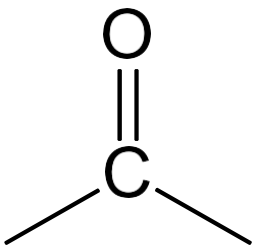
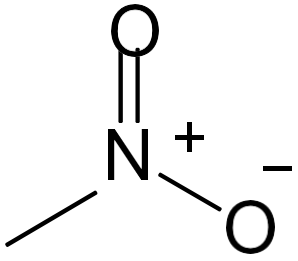
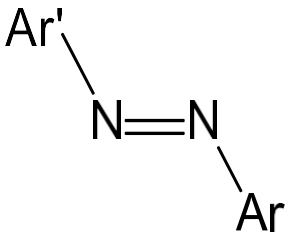


Why the Br left the compound and not the Cl ?? because the Br is better as a leaving group (larger size
And in general any carbon with an H and a GLG on it can undergo this type of reaction.



Reduction Reactions

هسا احنا بنعرف انه الهدف من metabolisim انه نزيد من polarity حتى يقدر يذوب مع المي ويطلع من الجسم مع urin , طيب عملية الاختزال بتقلل من polarity ليش اعتبرناها وحدة من عمليات metabolisim ؟؟ لانها بتمهد الطريق لعملية conjugation (phase 2) كيف يعني ؟؟
يعني انها بتحول F.G ما بتقدر تعمل conjugation ل F.G قادرة على ذلك (رح نفهم اكثر بس ندرس phase 2)

carbonyl	nitro	azo
		 Ar: aromatic moiety

All of previous functionalities can undergo reduction reactions, and we are going to discuss each one of them.

Carbonyl compounds.

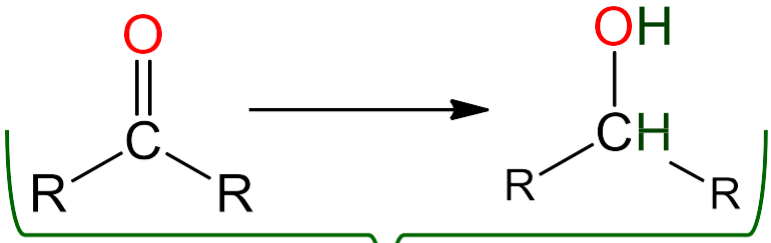
من وين بنقدر نجيب الالديهايد والكيتون ؟؟ يا اما من ال drug او من تفاعلات ال metabilisim(oxidative deamination)

Just opposite of oxidation reactions.

COOH > CHO> CH2OH

This is in case there is carboxylic acid

It is reduced to an aldehyde first and then to a primary alcohol



If there is a ketone, then it is reduced to a secondary alcohol

You might be asking why am I making a high polar compound less polar by reducing it??

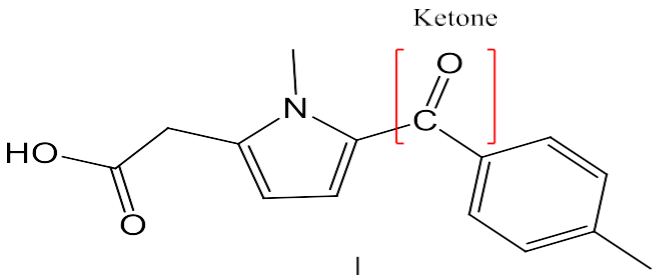
The answer to this is, to prepare it to PHASE II reaction as we will see in a bit

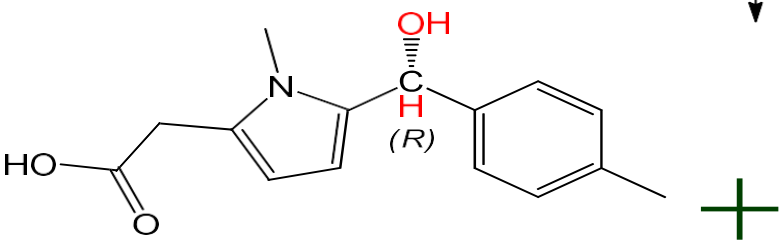
When the ketone is reduced to secondary alcohol

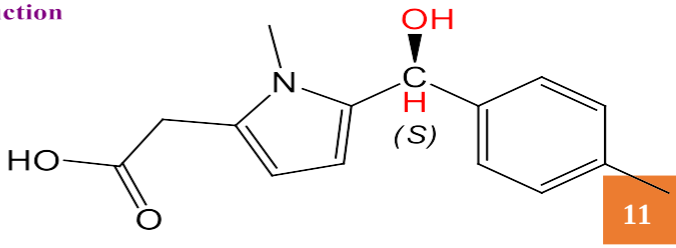
It might create a new chiral center

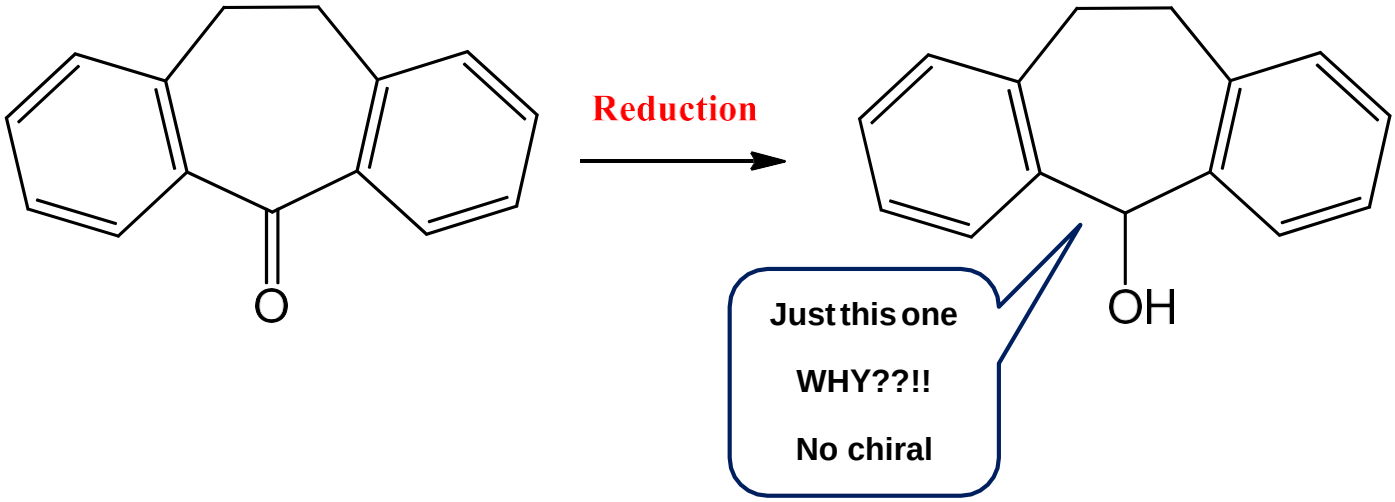
So pay attention to the R & S

Both are possible products









لازم تعرفوا انه لما نعمل **reduction** للكيتون بعطينا كحول ثانوي ورح يكون عنا **chiral center** ورح يكون عنا **s** او **R** لكن شوفوا اخر مثال ما طلع معنا مركبين ليشلانه الكربونة اللي هون مش كايرال بالتالي ما رح يكون عنا **R** او **S**

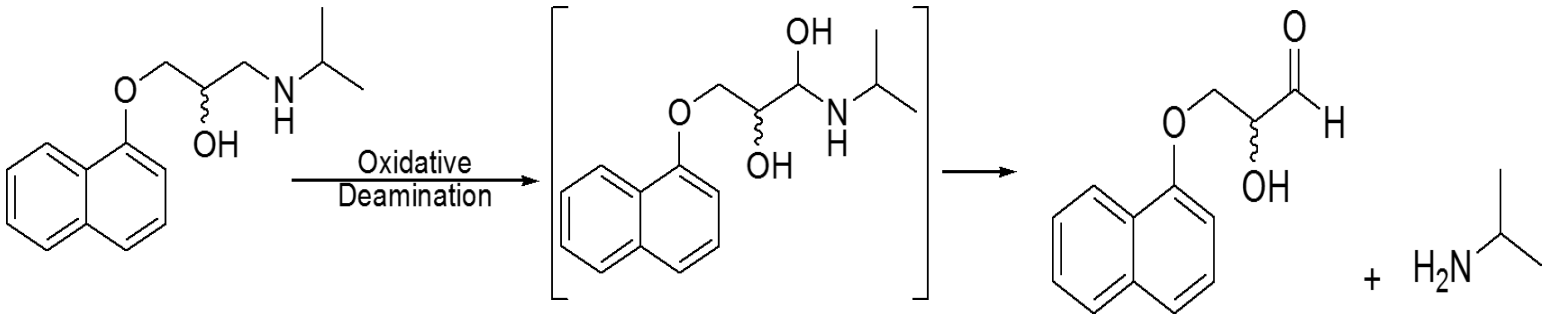
Reduction of keton is stereoselective

يعني ممكن نحصل على **R** لحالها او **S** لحالها او **mixture from R and S**

Now, drugs with carbonyl moieties come from deamination reaction.
Secondary & Primary amines undergo deamination reactions where the amine group is kicked out of the drug and the drug end up with carbonyl moiety in it.

هون تذكير لمعلومة انه لما نعمل **deamination** بعطينا الكربونيل والمجموعة الثانية بتطلع امين زي هون

اما لما نعمل **dealkylation** الكربونيل بتطلع و الأمين بتضل جزء من **drug**



After the deamination reaction

A carbonyl is formed.

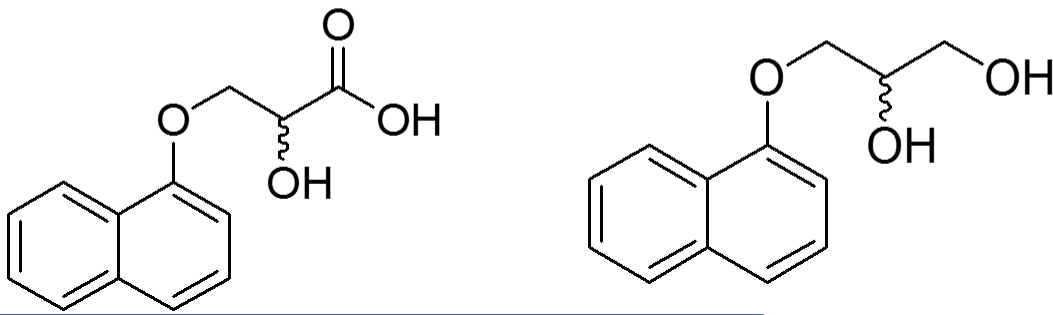
This carbonyl has 2 routes

Oxidation to a carboxylic acid

(Major)

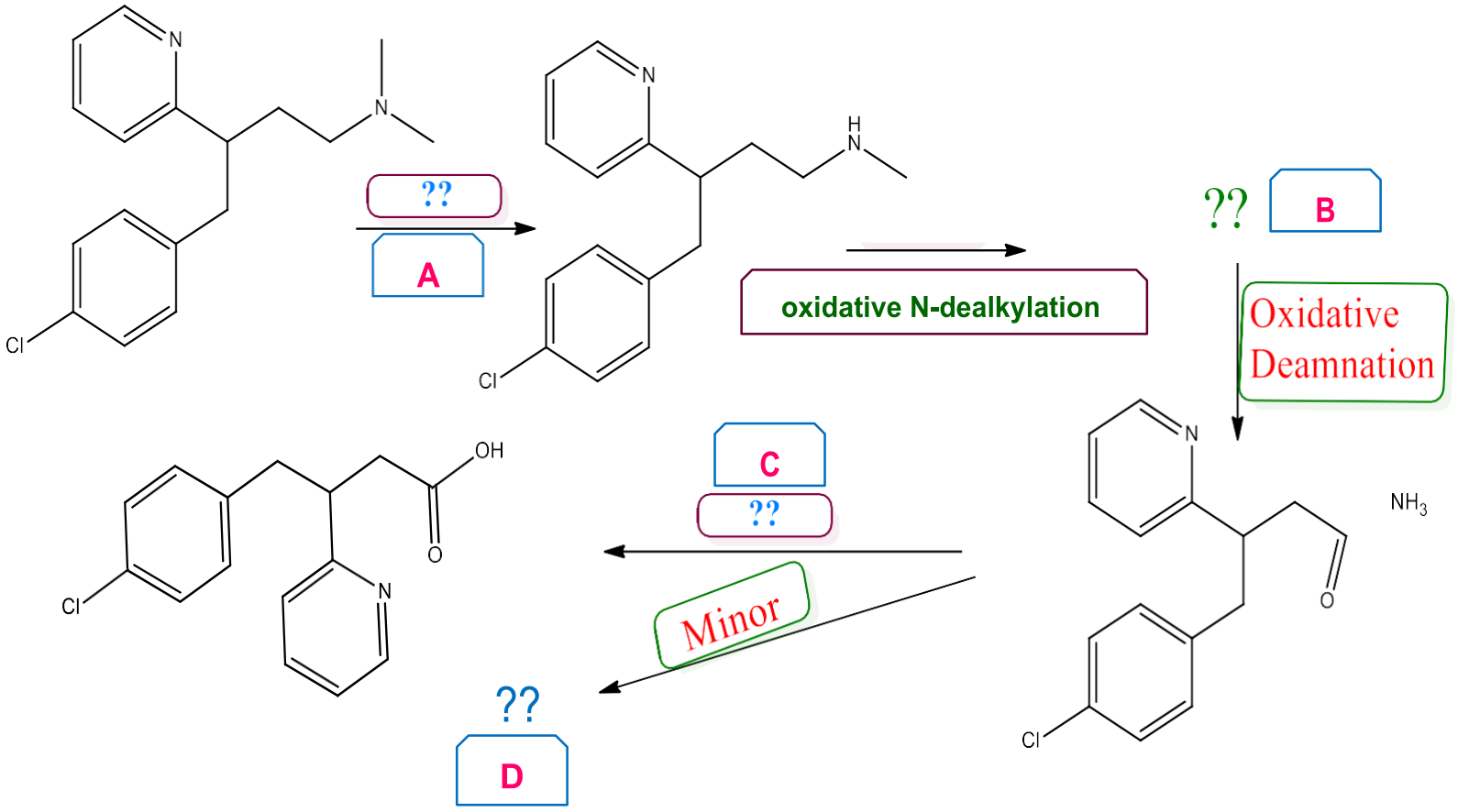
Or reduction to an alcohol

(Minor)



Oxidation is most of the times the major product and the reduction is the minor

الخلاصة لما نعمل deamination بنتج مركبين major=oxidation و minor=reduction



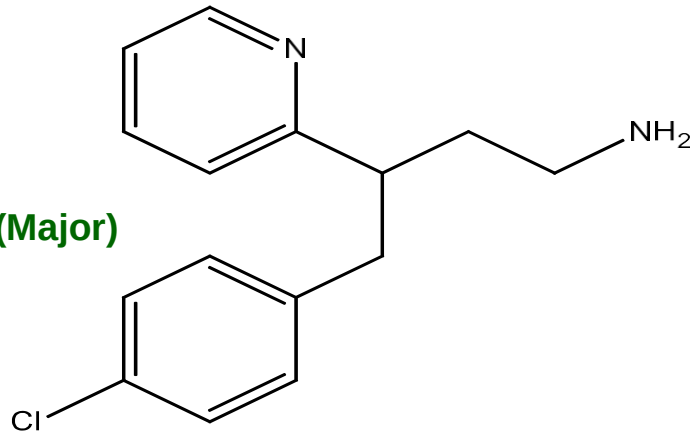
Complete the scheme. (expect something like this in the exam, it not complicated)
Look at the starting material, and compare it with the product after it.
The tertiary amine group become a secondary amine and one of the methyl groups are gone, \\ so the reaction is oxidative N-dealkylation

So (A) is: oxidative N-dealkylation **(B) since the reaction is oxidative N-dealkylation**

(C) notice the compound before and the compound after

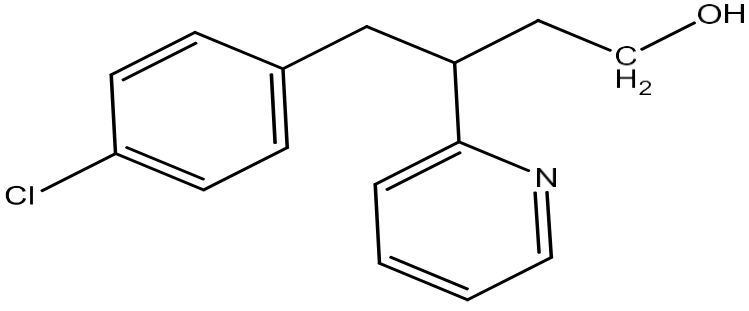
The reactant is an aldehyde while the product is

Carboxylic acid. So the answer should be Oxidation (Major)



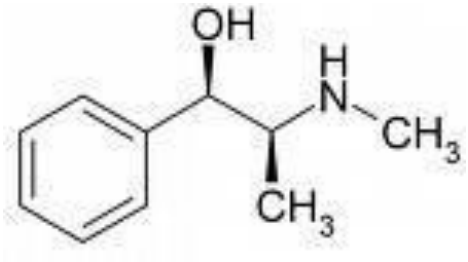
(D) from the aldehyde, a there is a minor product

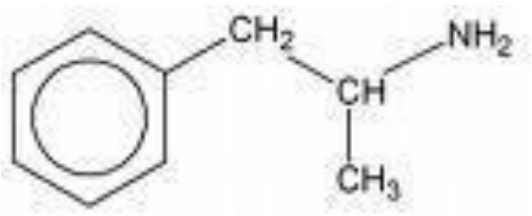
We said that it is the reduction product.



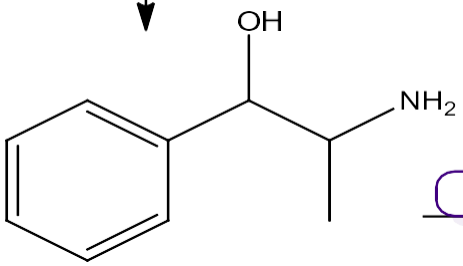
هاد السؤال جامع اكثر من فكرة حلوة للتدريب سهل بس ركزوا

compounds undergo oxidative deamination to ketone and then reduction to secondary alcohol



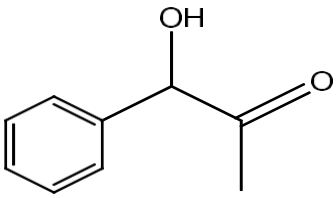


Oxidative N-dealkyation



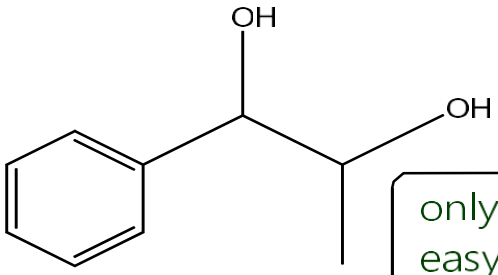
ephedrine

Deamination



NH_3

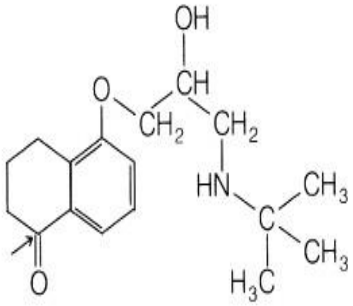
Reduction

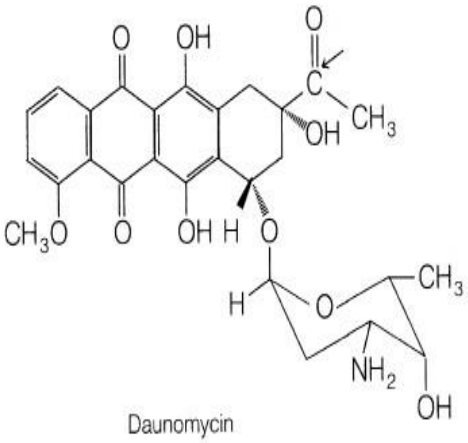


only reduction reaction product, because it is not easy to oxidize ketones to carboxylic acid

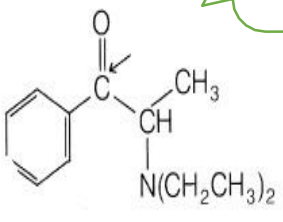
also remember that there are the S and R isomers

Search for the arrow

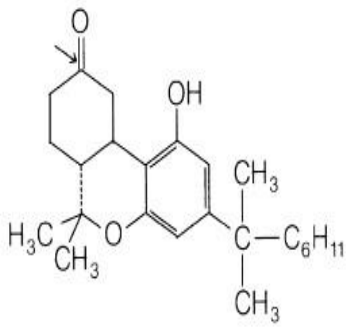


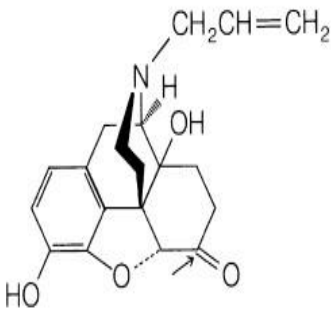


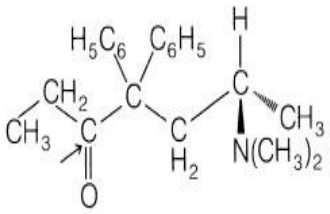
Daunomycin

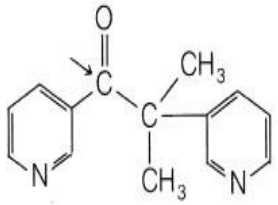


Diethylpropion







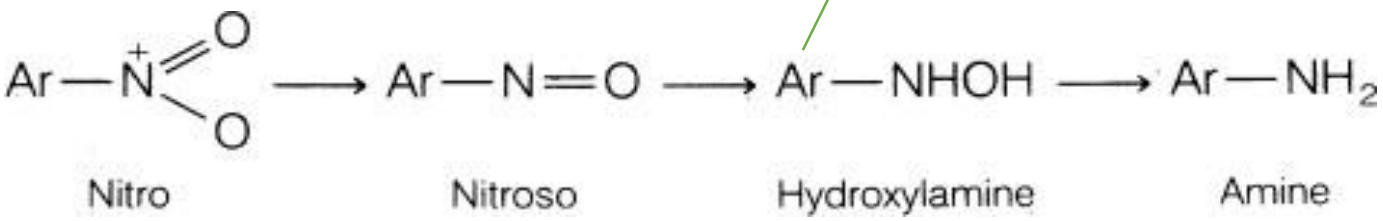


Nitro compounds

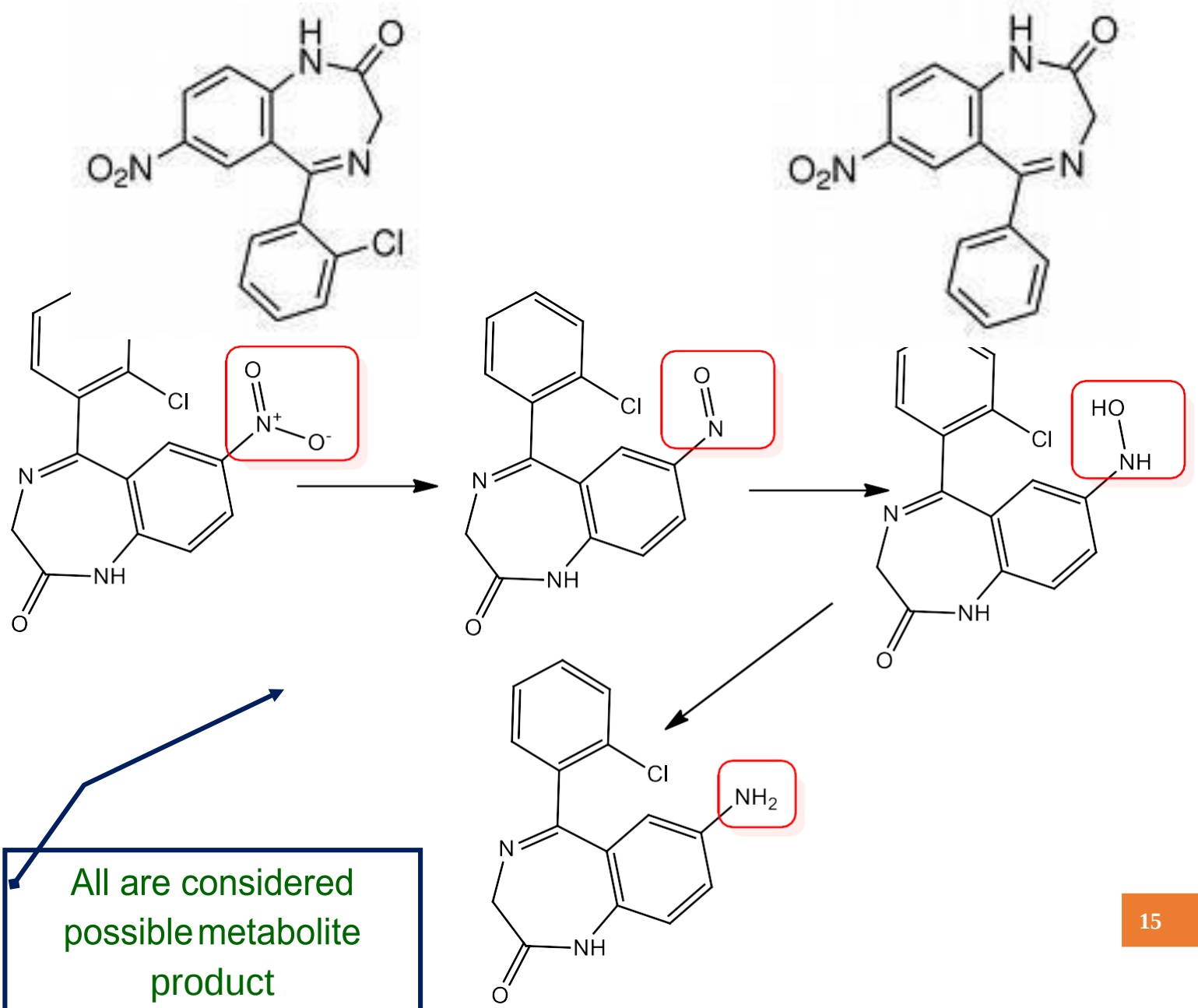
- The **end product is primary amines.**

Aromatic

Aromatic nitro to nitroso to hydroxylamine to amine



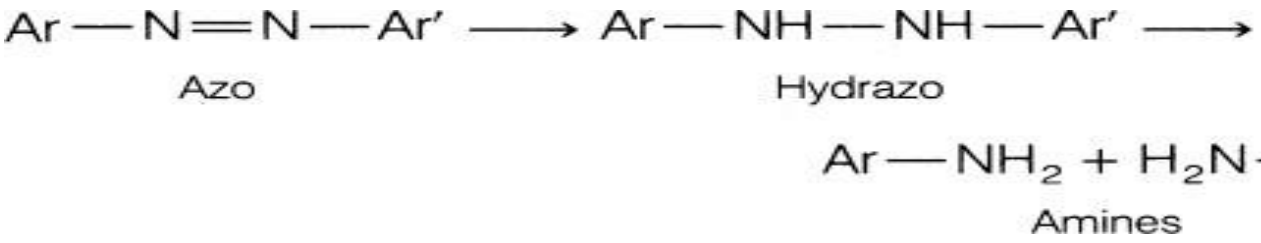
تتذكروا النايترو كيف حصلنا عليه ؟! اول اشي من برايمري امين عملناله oxidation صار هايدروكسيل امين بعدين nitroso بعدين نايترو والعكس تماما رح يصير عنا بال nitro , اول اشي رح نبلش بالنايترو بنعمله reduction بصير nitroso بعدين بنكمل لحتى نوصل لل amine , ف reduction عملية عكسية لل oxidation

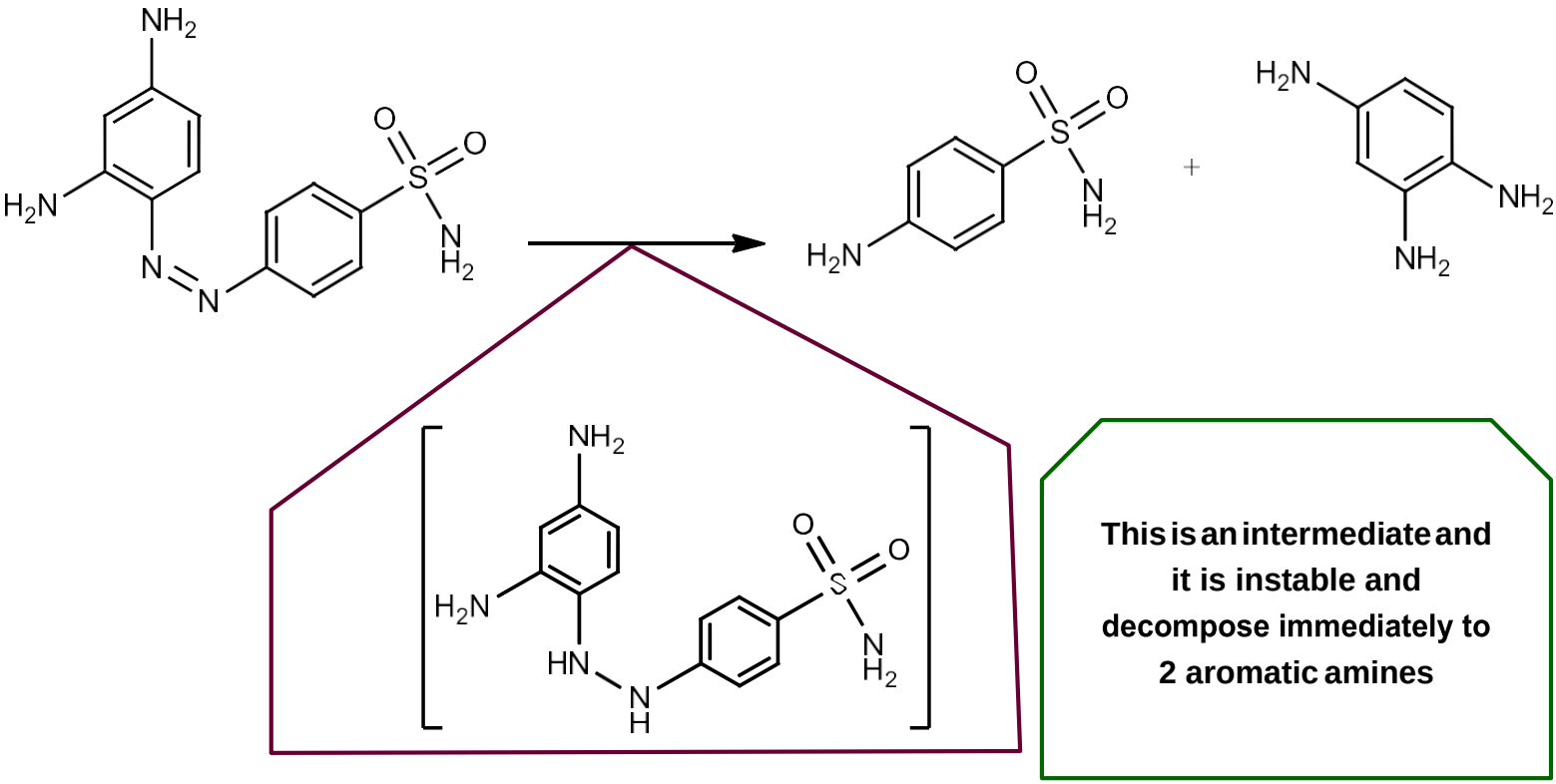


Azo compounds

Aromatic azo to hydrazo to cleavage to two aromatic amines

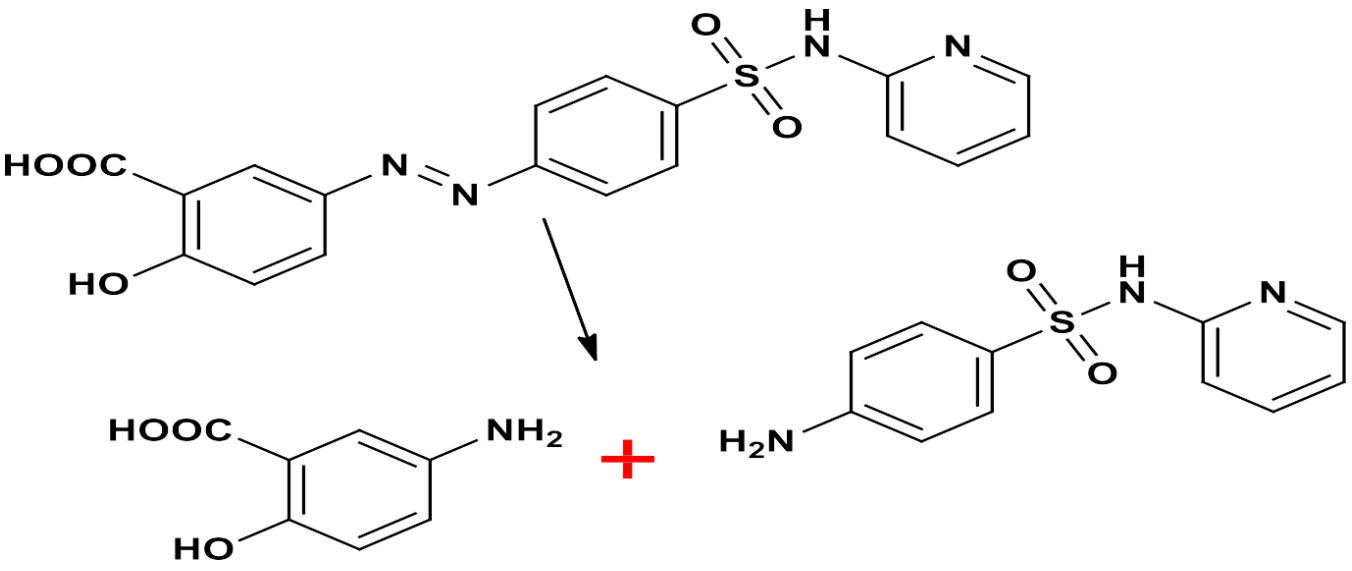
ال Azo عبارة عن 2N بينهم دبل بوند والرابطة الثالثة بتكون عبارة عن aromatic





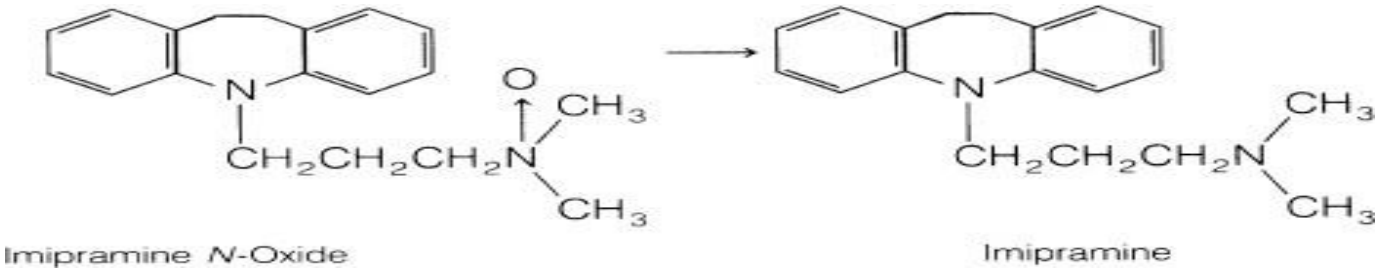
This is an intermediate and it is instable and decompose immediately to 2 aromatic amines

Azo بصيرلها reduction بتعطينا hydrozo وهو عبارة عن intermediate والناتج 2 amines



Other reduction reactions.

***N*-Oxide to tertiary amines**, opposite of the oxidation of aromatic amines.
reduces the polarity of the tertiary amines, so reduce excretion

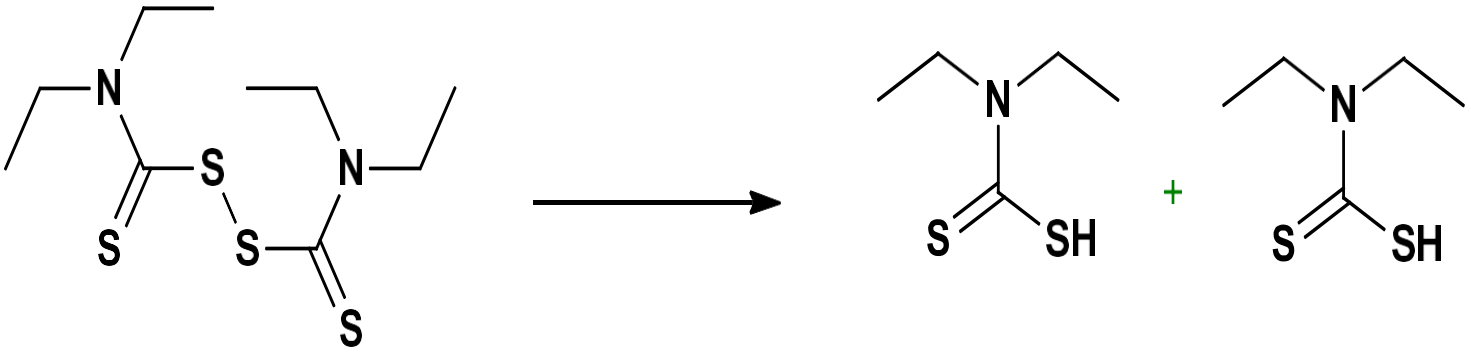


بكل بساطة N-oxid بنسحب منها الاكسجين بتصير tertiary amine

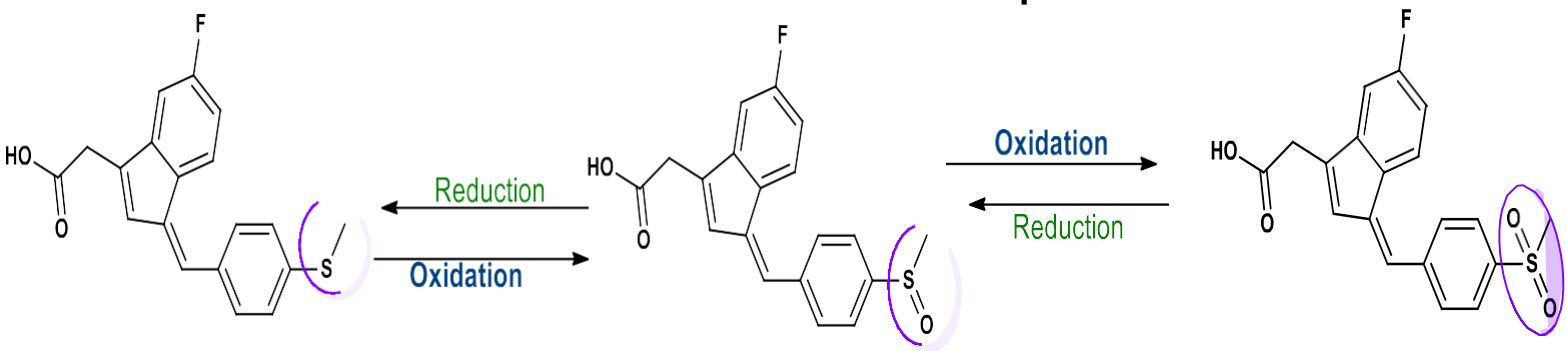
Disulphide reduction

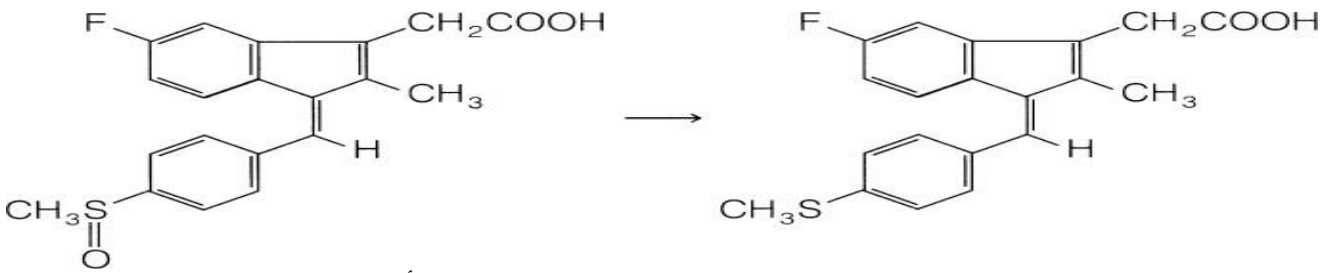
Where the sulfide bridge is broken (S-S) bond to SH and SH

The S-S form is the oxidized form, while the SH form is the reduced form.



Also the oxidation of sulfide to sulfoxide and then sulphone.

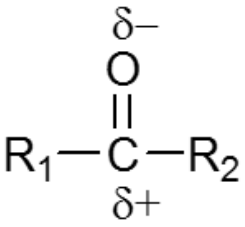




في رابطة جديدة لازم تعرفوها اسمها sulfide bridge وهي عبارة عن S مرتبطة برابطة أحادية مع S ثانية وهاي بتكون بحالة ال oxidized واللي بصير بال reduction انه بنكسر هاي الرابطة وبنعطي كل S ذرة H

Hydrolytic Reactions

The metabolic products that are formed from this reaction (carboxylic acids, alcohols, phenols, and amines) generally are polar and functionally more susceptible (عرضة ل) to conjugation and excretion than the parent ester or amide drugs



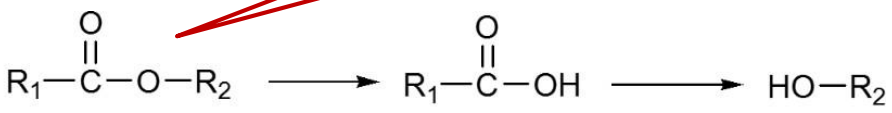
R_1	R_2	Name	Susceptibility to Hydrolysis
C	O	Ester	Highest
C	S	Thioester	
O	O	Carbonate	
C	N	Amide	
O	N	Carbamate	
N	N	Ureide	Lowest

These hydrolytic reactions are the same ones as the in Chapter 7

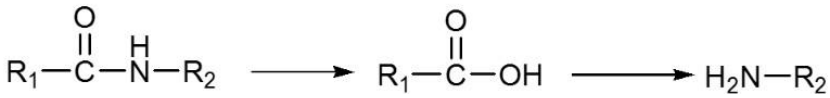
Basically you have to remove the group attached to the carbonyl carbon and add OH instead

Removed the OR2\NHR2 and replace it with OH

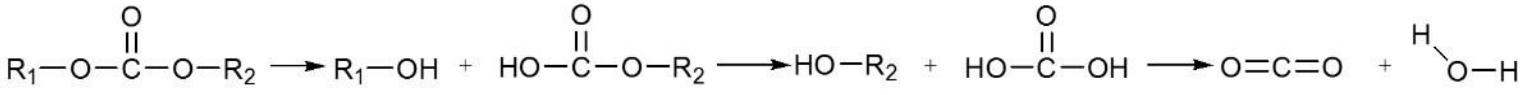
Ester hydrolysis



Amide hydrolysis (slower)



Carbonate hydrolysis



Carbonate — Carbonic acid derivative — Carbonic acid

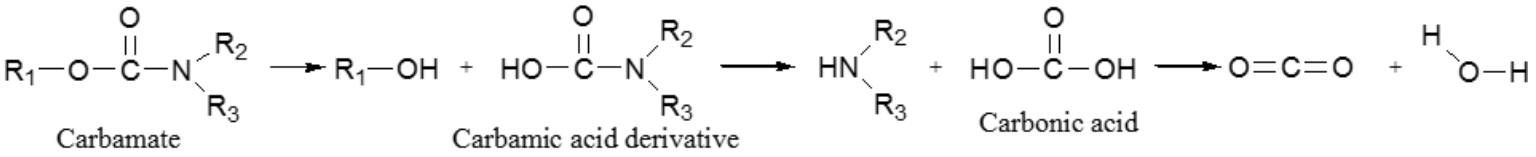
In here the reaction is step reaction

The 1st, OR1 is removed and the 2nd OR2 is removed

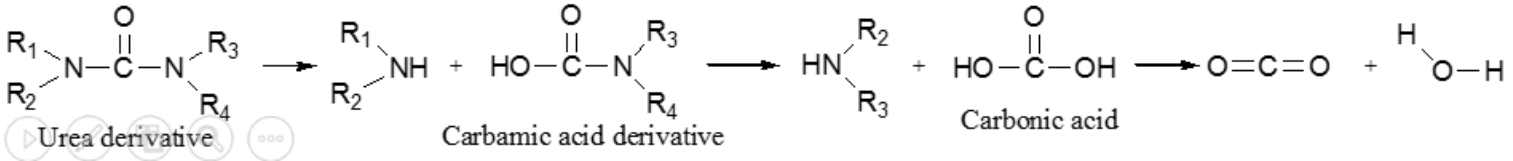
In both cases an OH was placed

The final product is the Carbonic acid and CO2 and H2O

Carbamate hydrolysis

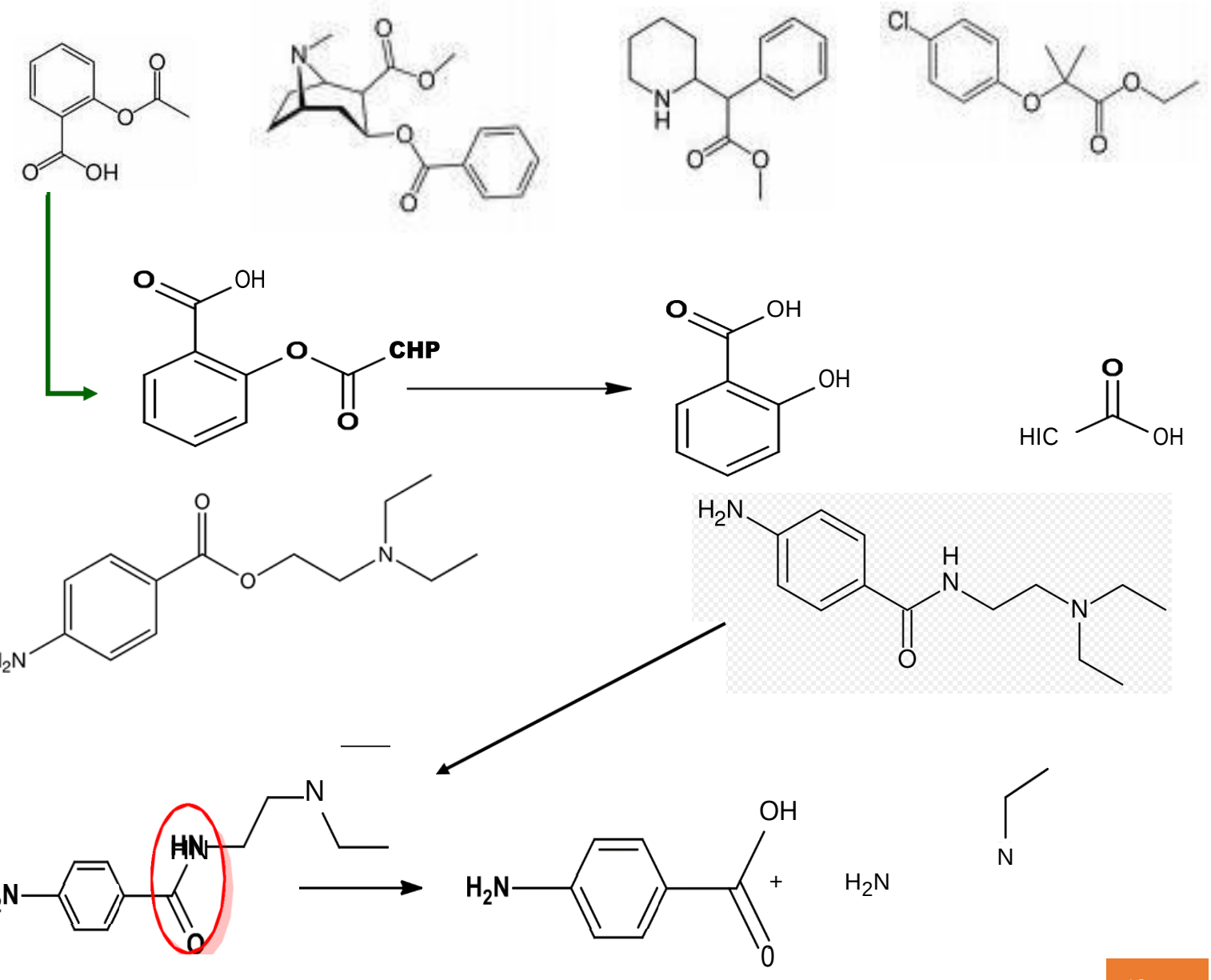


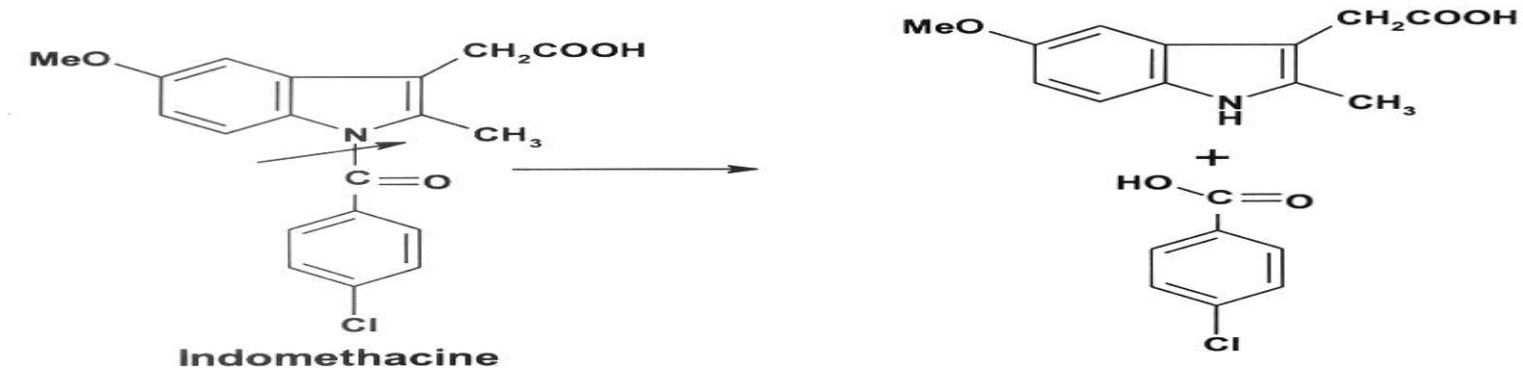
Urea hydrolysis

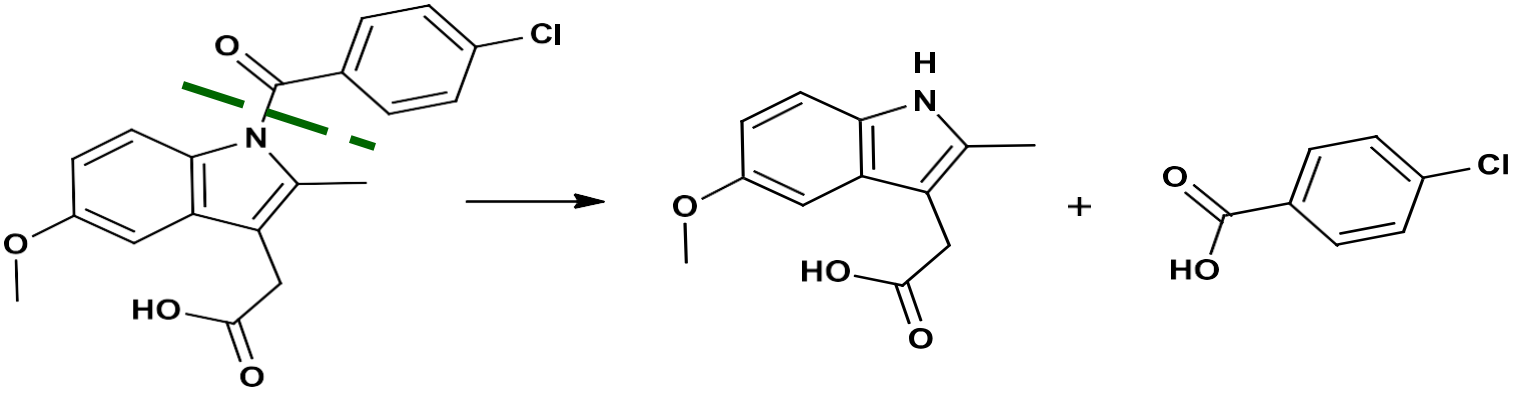


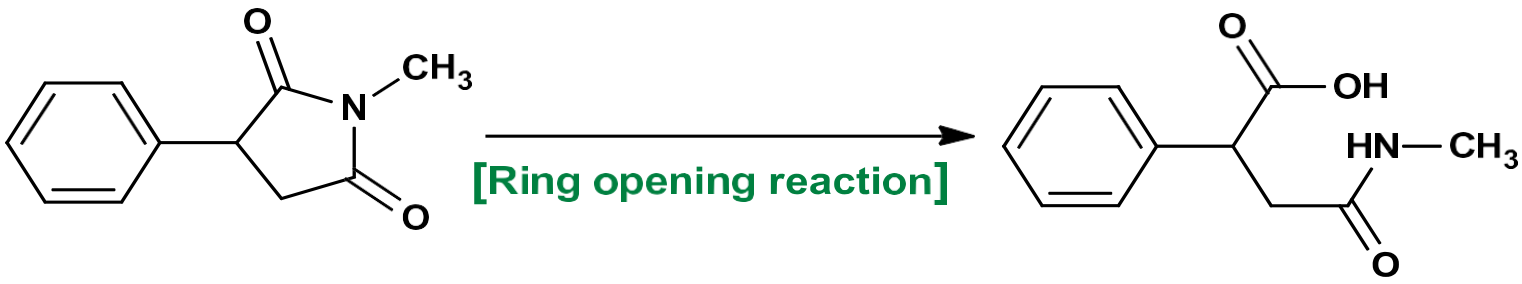
((حدوث هاد التفاعل على carbonat وcarbamate و urea الدكتورة ذكرتهم ذكر بالمحاضرة يعني ما شرحتهم بس خليناهم للاحتياط ما بتعرفوا ممكن تجيبهم مدام حكتهم بالمحاضرة))

Same as the carbonate hydrolysis









Remember, we break the bond between the carbonyl carbon (C=O) and the O\N from the OR\NR2 part.

يعني الرابطة اللي بنكسرها بتكون بين كربونة الكربونيل والجزء الثاني اللي متصل فيها (مثل الاكسجين او النيتروجين)

PHASE II: CONJUGATION Reactions

The main reactions is conjugation, which is to attach a highly polar group to the Drug and thus making it more hydrophilic and susceptible to excretion. There are other to reactions for Phase II, and they are Methylation and acetylation reactions.

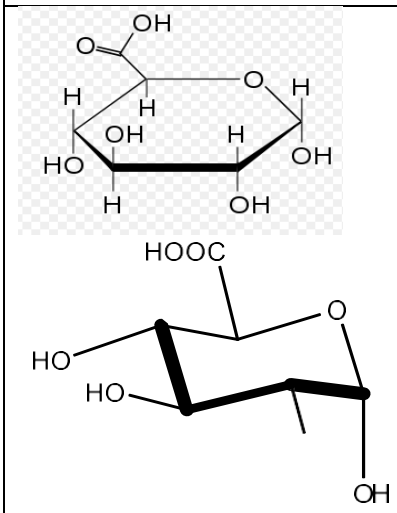
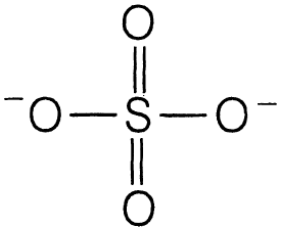
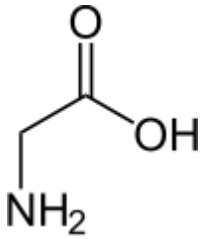
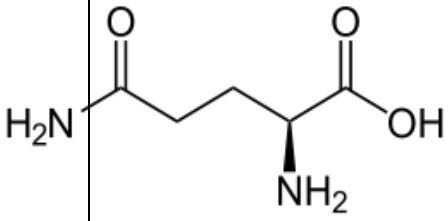
These 2 reaction don't increase the polarity, exactly the opposite, it decrease it, so how is this helpful??

What these reactions do (Methylation and acetylation) is to inactivate the drug and so it can't react with anything in the body and thus can't do harm.'

CONJUGATION

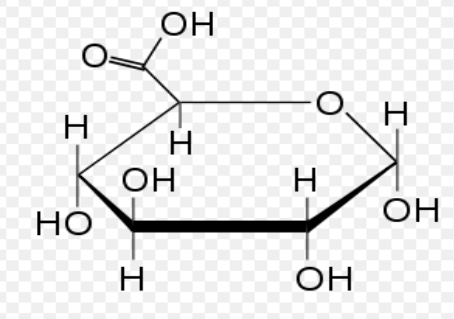
Conjugated products are relatively excretable, biologically inactive and non-toxic

Conjugation reaction can happen directly to a parent drug or phase I metabolite product.

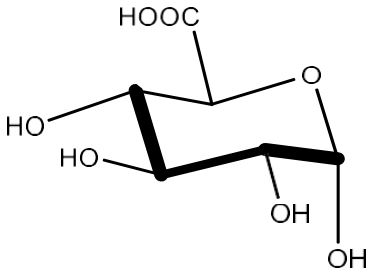
Glucuronic acid	Sulfate	Glycine	Glutamine
	 **SO4-** **-SO^-_3 (when attached to a drug)**		

MEMORIZE

Glucuronic acid conjugation



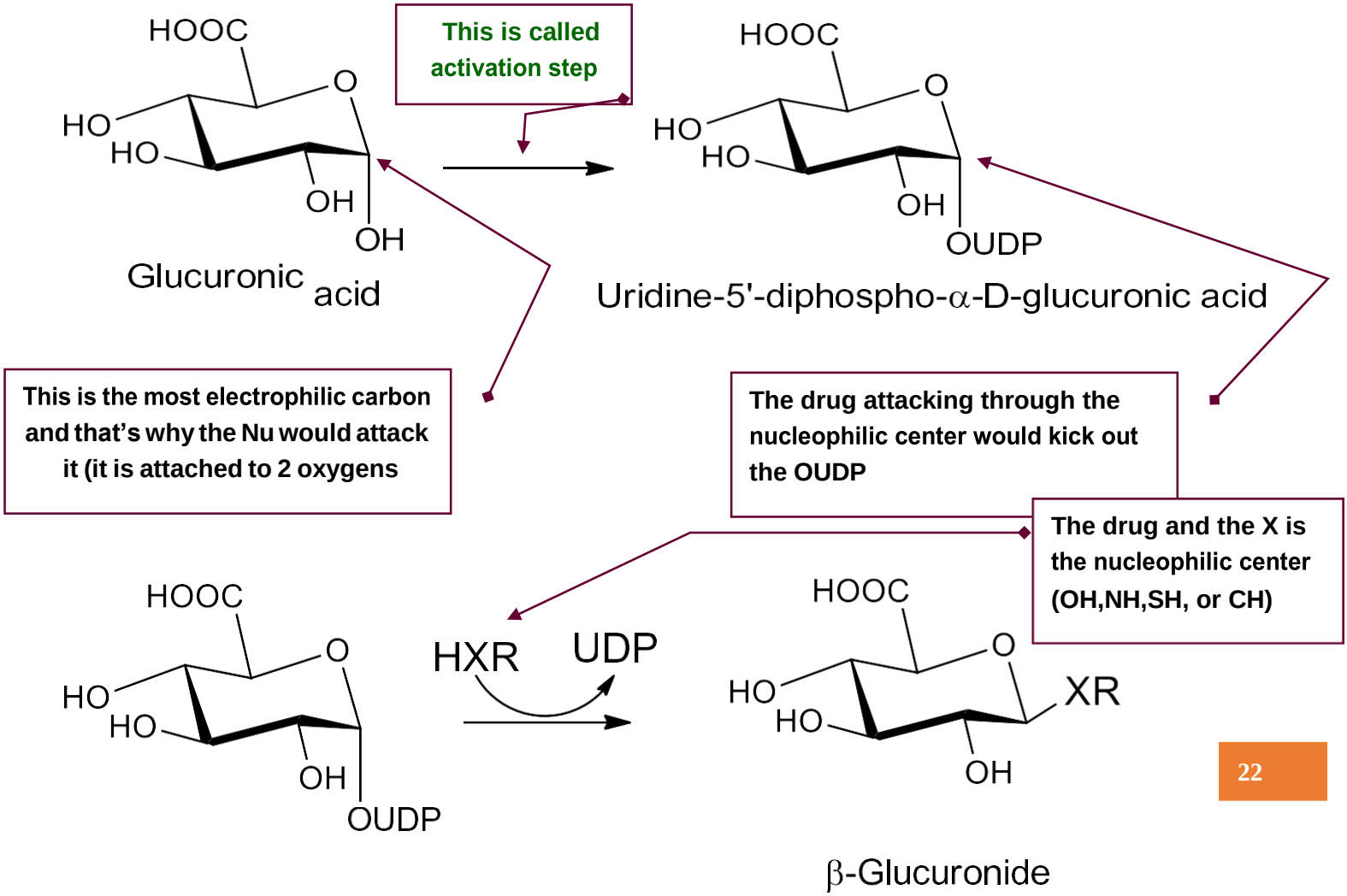
Must MEMORIZE



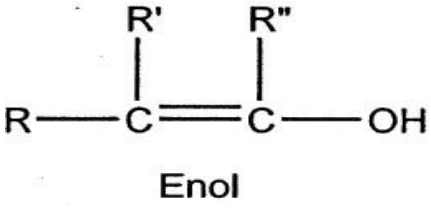
for glucuronic acid (GA, هاذ اختصار من عندي) to be attached to a drug the drug must have OH, NH, SH and a CH where the H attached to the C is acidic (means that the (-) formed on the C is stable and thus can formed.

Why is that?? Because the way that the GA is added to the drug is through nucleophilic attack by the drug on the electrophilic carbon in the GA.

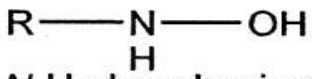
Before the attack happen the GA must have a GLG for the reaction to proceed. And that why the first step is to create a GLG >> this occur by adding a UDP (uridine-5-phosphote)


This is called activation step
Glucuronic acid
Uridine-5'-diphospho-α-D-glucuronic acid
This is the most electrophilic carbon and that's why the Nu would attack it (it is attached to 2 oxygens
The drug attacking through the nucleophilic center would kick out the OUDP
The drug and the X is the nucleophilic center (OH,NH,SH, or CH)
HXR
UDP
β-Glucuronide

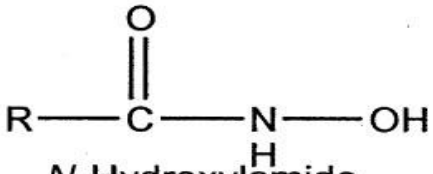
In general as for the O- glucuronation (when the O attack the GA)
It mostly occur to hydroxy (OH) and carboxy (COOH) groups and less frequent to enols, *N*-hydroxylamines, and *N*-hydroxylamides



Enol

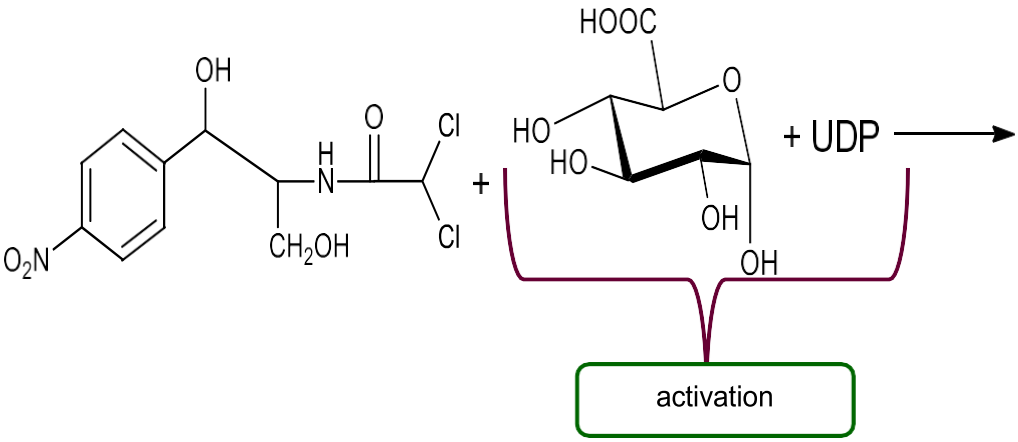


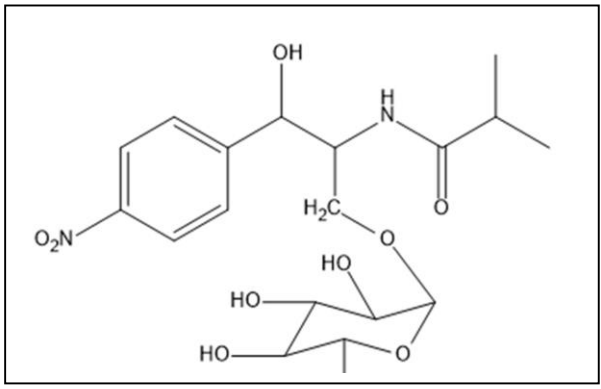
N-Hydroxylamine



N-Hydroxylamide

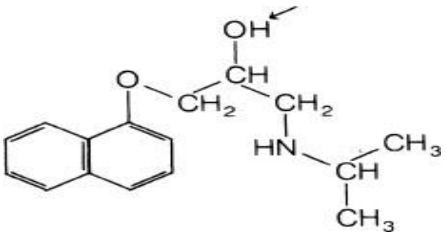
يعني انه التفاعل هاد بيحصل بالعادة للمركبات المحتوية على COOH OR OH اما المركبات الثانية فهو اقل حدوث

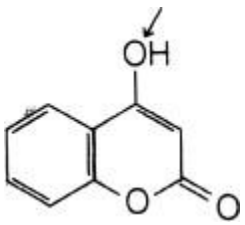


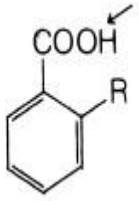


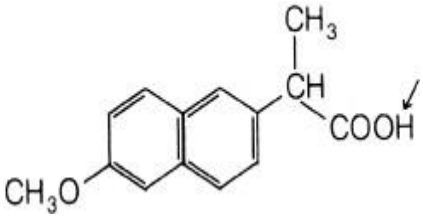
هون الكربونة بتكون هي الالكتروفايل ف ال N,O,S بهاجموا الالكتروفايل اللي هي الكربونة

- **Notice that position of the OH group in the GA, before the addition it was axial (α-GA) and after the attack the position became equatorial (β-GA)**
- **This indicate that this is an SN2 attack.**



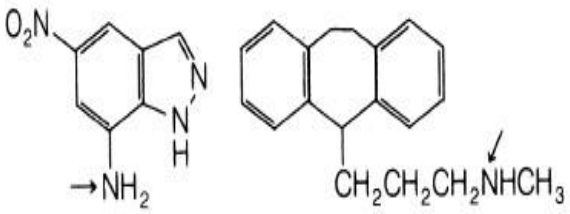


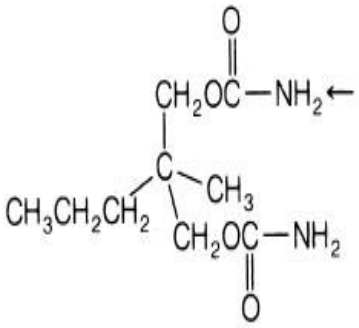


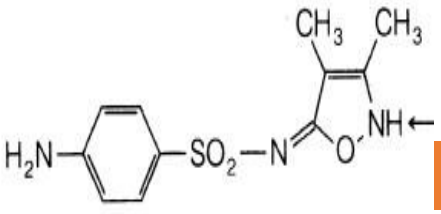


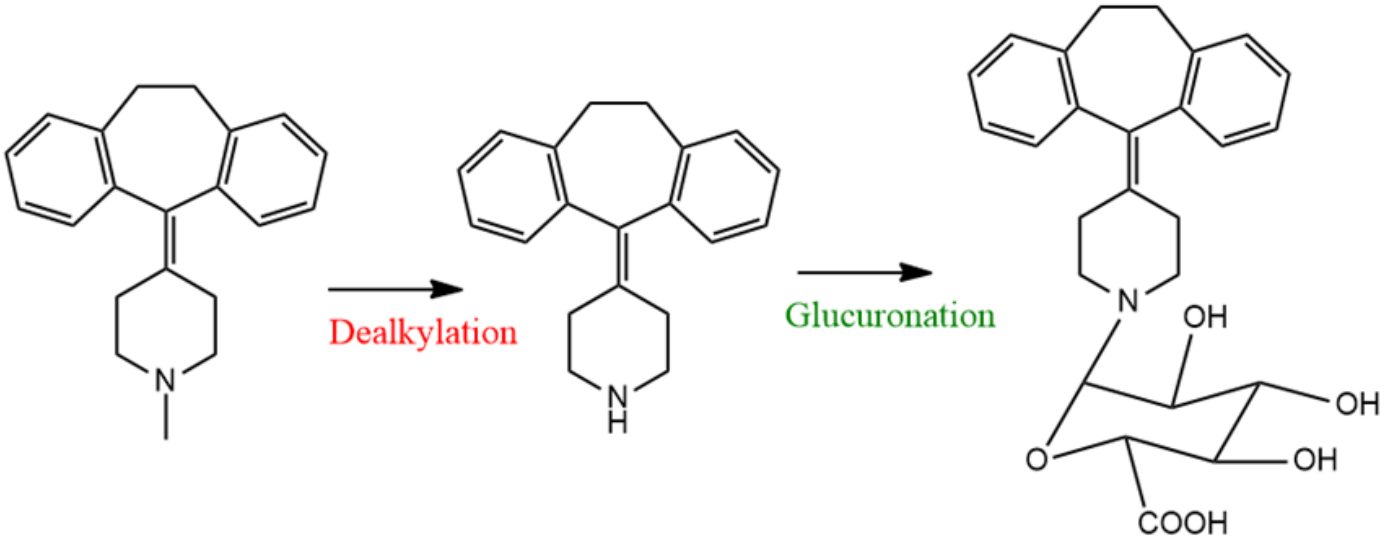
Remove the H and a GA group

N-glucuronation



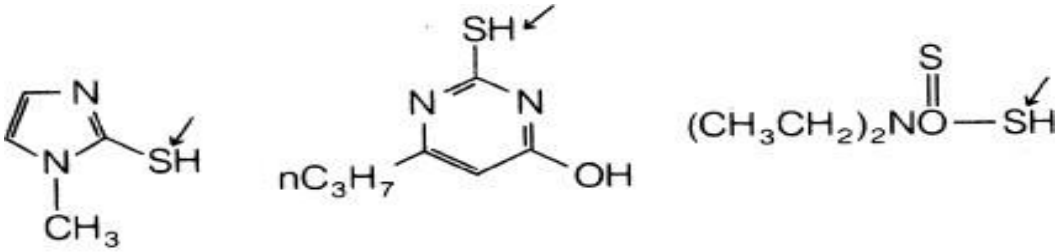




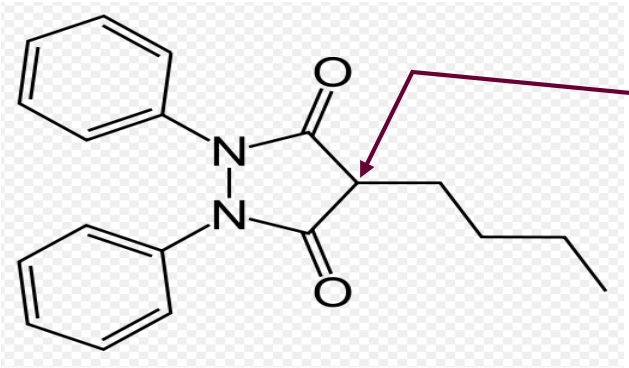


Pay attention to the conversion from alpha to beta

S-glucuronation

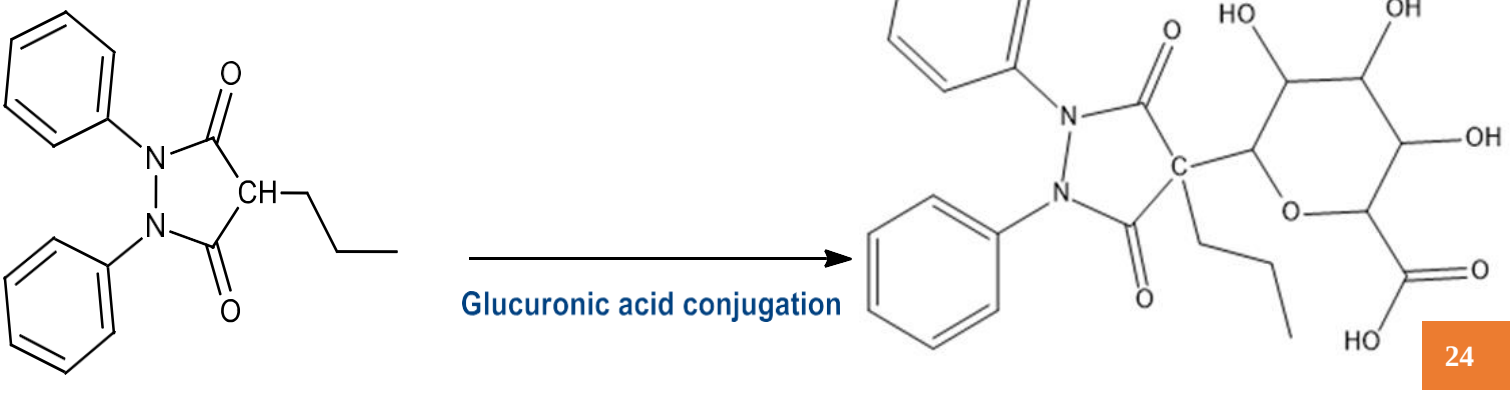


C- glucuronation: there has to be an acidic hydrogen



When the H leave the compound the (-) formed would be stabilized by resonance so the H is acidic

And the carbon can undergo glucuronation

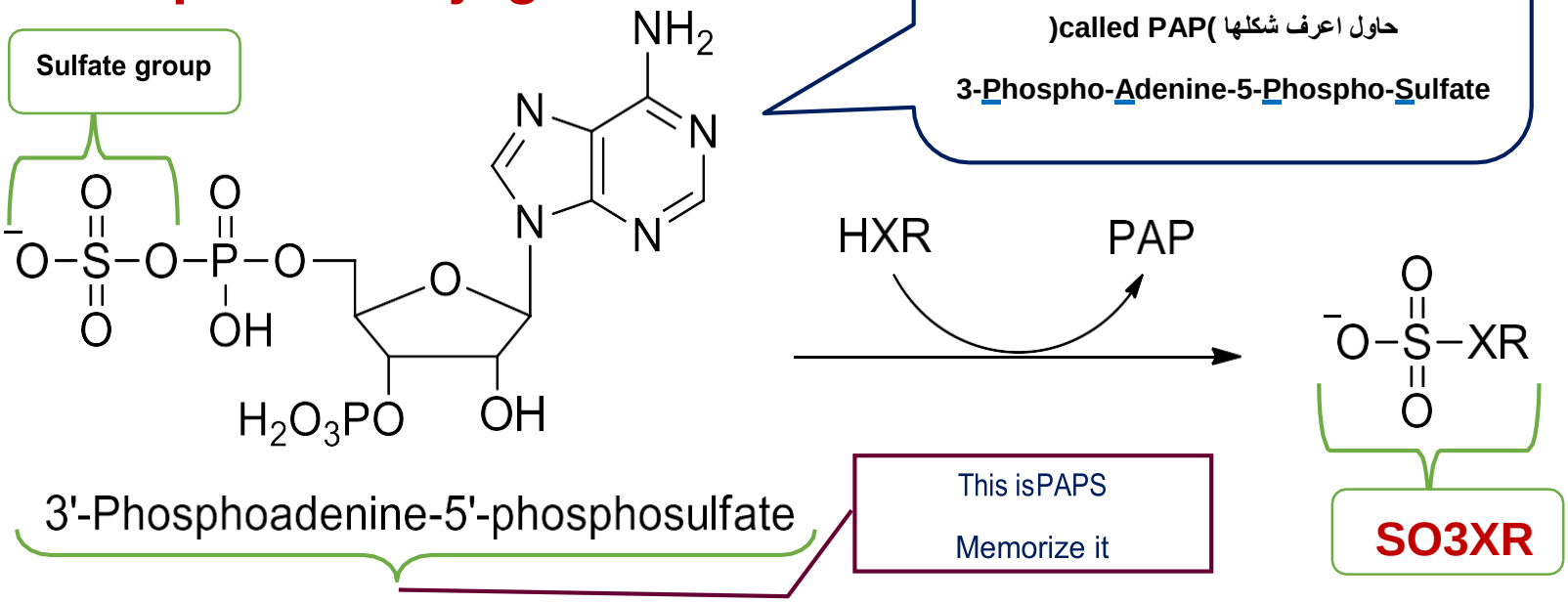


Sulphate conjugation

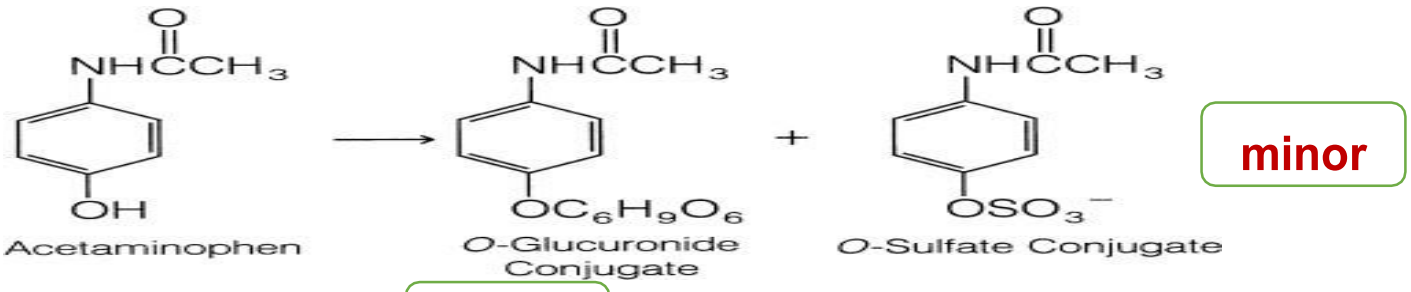
The rest of the group is to activate the sulfate group >make it better GLG (like the UDP in GA)

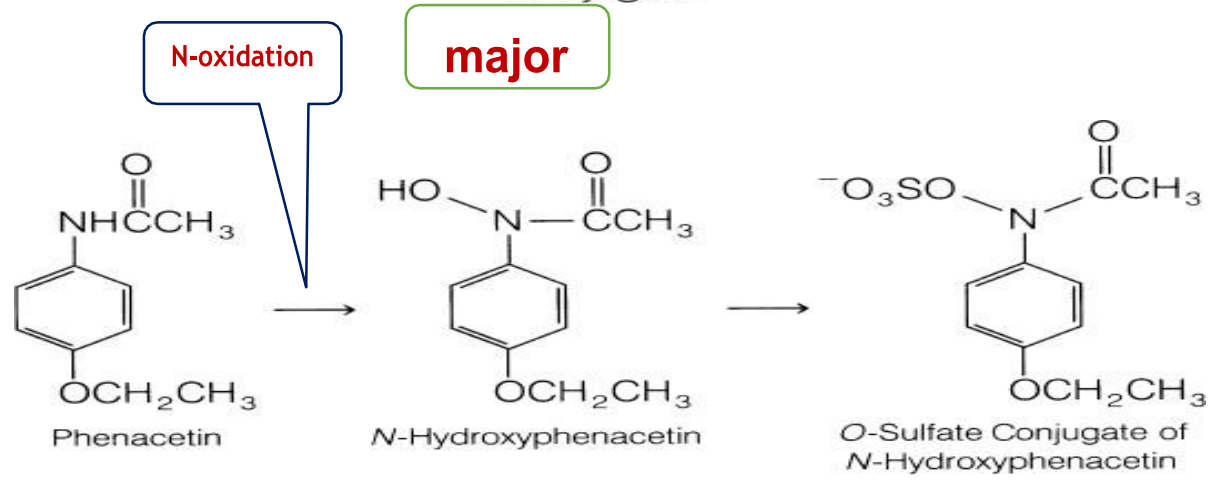
)called PAP(حاول اعرف شكلها

3-Phospho-Adenine-5-Phospho-Sulfate

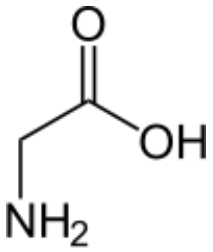


- **Sulphate conjugation Lead to water soluble and inactive metabolite, but some O-sulfate and**
***N*-hydroxy compounds give toxic metabolites (the aromatic amines and amides).**
Sulfate comjugation occur to (O, S, N) but not C
*****There is a competition between GA and sulfate conjugation, the GA conjugation though is the dominant one in adults, simply because the concentration of GA in the body is higher.**
In new born babies the sulfate conjugation is the dominant one, not because the concertation of the sulfate is more, no
Because the enzyme responsible for the GA conjugation is not mature in babies



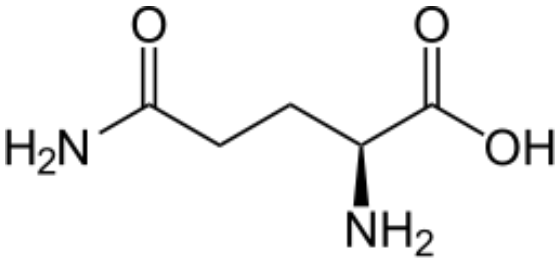


Aminoacids conjugation



Glycine

Must MEMORIZE



Glutamine

In amino acids, the carbon attached to the COOH and NH3 is called the alpha carbon

The alpha is attached to an H as well and this is for all the amino acid

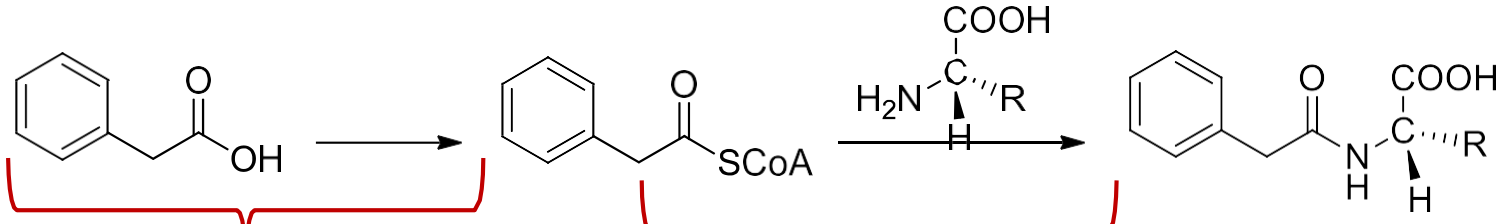
The only difference between the amino acids is the R group (side chain) >> for glycine the R is an H and for the glutamine the R is (CH2CH2CONH2)

If you see a COOH in the drug, then it is to be conjugated with an amino acid

in here the drug is going to be activated and not the added group like the sulfate and GA; because the OH in COOH is a bad leaving group

- **The process of conjugation is as follows:**
- **Activation of the carboxylic acid containing compound to form Acyl-CoA.**

Acylation of glycine or glutamate by *N*-acyltransferase which occur in mitochondria of liver and kidney

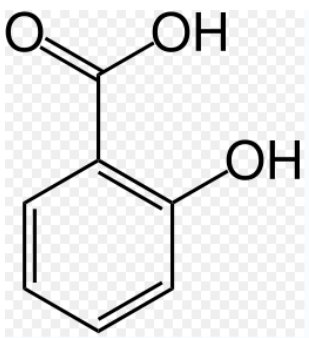


Activation of the drug

glycine conjugation

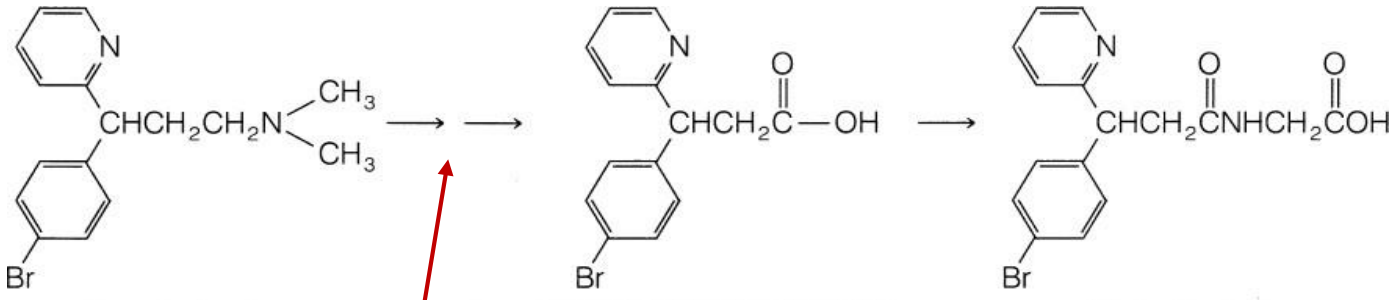
the conjugation (الارتباط) occur from the N of the amino acid

remove the OH and add the amino acid from the N terminal

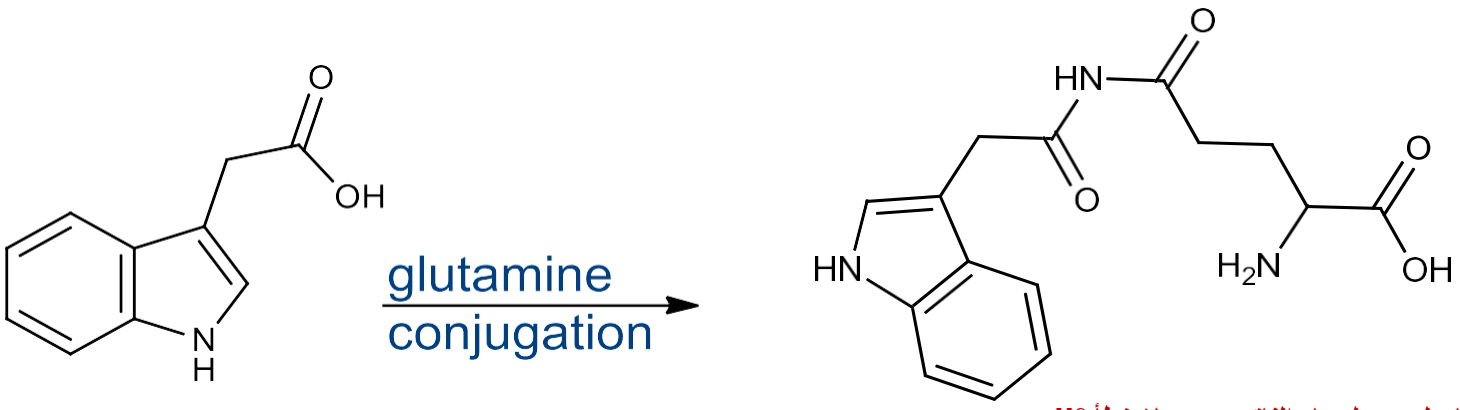


Conjugation from here

COOH



In here 2 N-dealkyation and then deamination occurred and resulted in an aldehyde that got oxidized which got us to our compound



برأيكم يا حلوين هل هاد الناتج صح ولا خطأ ؟!!
اكيد خطأ , طب ليه ؟؟
لانه لازم يرتبط المركب مع الالفا نيتروجين او الالفا امين (المرتبطة بالالفا كربون) مش بالنيتروجين تاعت الاميد زي ما هو موجود بالمركب

GSH (glutathione), (mercapturic acid conjugates)

It is a tripeptide (3 amino acid chain), that is composed from (glutamine-cysteine-glycine)

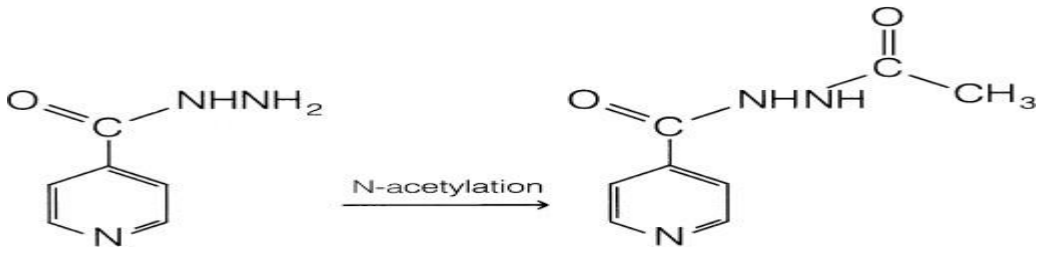
The cysteine has in his R side chain an SH (thiol group) and this is the Nucleophilic center in GSH

بكل بساطة بنشيل OH وبنحط بدالها SG

Acetylation &Methylation

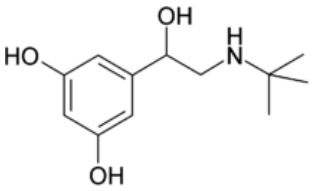
Add an acyl group (CH3-C=O) or a methyl group (CH3) on OH and NH2 and SH, as we remove the H and add the acyl or methyl.

Acyl or Methyl بنشيلهم وبنحط SH,OH,NH وين ما عنا

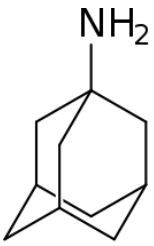


Remove the H and the acyl group

Isoprenaline

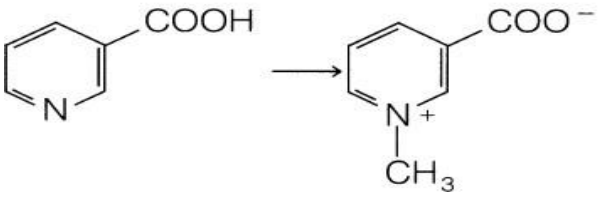


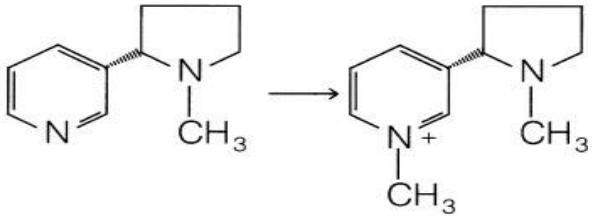
Terbutaline



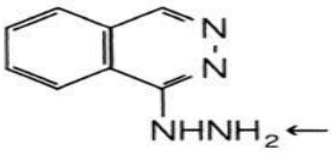
Amantadine

***N*-methylation present at heteroatom such as nicotine and nicotinic acid to give quaternary ammonium products**

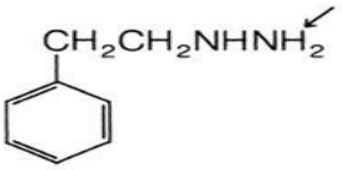




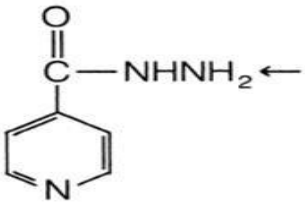
Hydrazines and Hydrazides



Hydralazine

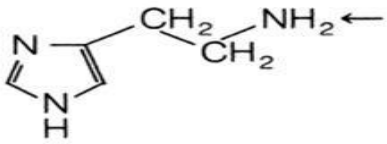


Phenelzine

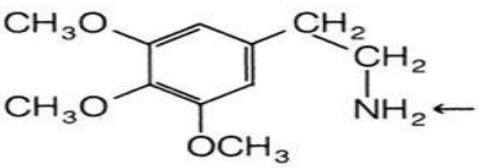


Isoniazid

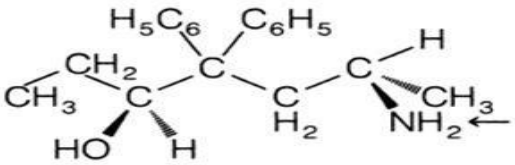
Aliphatic Amines



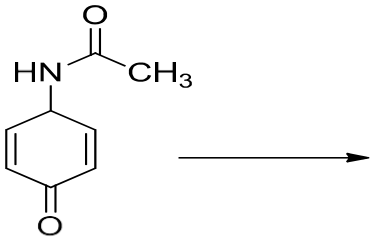
Histamine



Mescaline

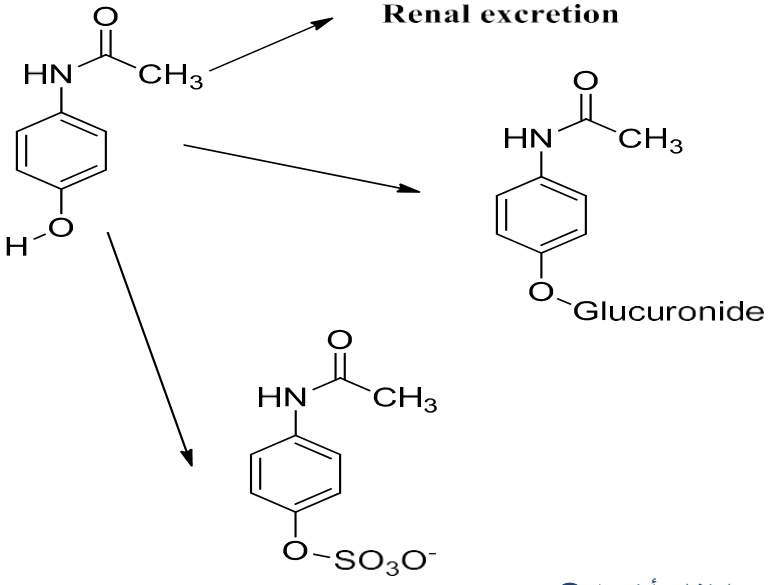


Bisdesmethyl Metabolite
of 3*S*,6*S*-α-(−) Methadol



N-acetylamindoquinone

Cause covalent binding with livercells, necrosis



Renal excretion

Glucuronide

Metabolism reaction IN General increases the polarity

As we have the methylation and acylation that decrease the polarity >> they inactivate the drug

وهيك بتكون خلصت مادتنا وأخيرا ☺
موفقين كلكم وفالكم العلامات العالية يارب ♥♥
اي سؤال بدكم إياه اسألونا

By Mohammad Al-Hamzeh